University of Alberta

Options for procedural sedation in paediatric patients requiring painful or anxiety provoking procedures in Emergency Departments

by

Lisa Maureen Evered ©

A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the requirements for the degree of Master of Science

in

Medical Sciences - Public Health Sciences

Edmonton, Alberta

Spring 2005

Library and
Archives Canada

Published Heritage
Branch

395 Wellington Street
Ottawa ON K1A 0N4
Canada

Bibliothèque et
Archives Canada

Direction du
Patrimoine de l'édition

395, rue Wellington
Ottawa ON K1A 0N4
Canada

0-494-08051-5

Your file Votre référence
ISBN:
Our file Notre reference
ISBN:

NOTICE:
The author has granted a non-exclusive license allowing Library and Archives Canada to reproduce, publish, archive, preserve, conserve, communicate to the public by telecommunication or on the Internet, loan, distribute and sell theses worldwide, for commercial or non-commercial purposes, in microform, paper, electronic and/or any other formats.

The author retains copyright ownership and moral rights in this thesis. Neither the thesis nor substantial extracts from it may be printed or otherwise reproduced without the author's permission.

AVIS:
L'auteur a accordé une licence non exclusive permettant à la Bibliothèque et Archives Canada de reproduire, publier, archiver, sauvegarder, conserver, transmettre au public par télécommunication ou par l'Internet, prêter, distribuer et vendre des thèses partout dans le monde, à des fins commerciales ou autres, sur support microforme, papier, électronique et/ou autres formats.

L'auteur conserve la propriété du droit d'auteur et des droits moraux qui protège cette thèse. Ni la thèse ni des extraits substantiels de celle-ci ne doivent être imprimés ou autrement reproduits sans son autorisation.

In compliance with the Canadian Privacy Act some supporting forms may have been removed from this thesis.

While these forms may be included in the document page count, their removal does not represent any loss of content from the thesis.

Conformément à la loi canadienne sur la protection de la vie privée, quelques formulaires secondaires ont été enlevés de cette thèse.

Bien que ces formulaires aient inclus dans la pagination, il n'y aura aucun contenu manquant.

Canada

Dedication

This thesis is dedicated to my husband, Curtis, and our boys, Jacob and Isaiah. I am eternally grateful for Curtis' love, support and encouragement. Our babies, who were born while I completed this project, give me endless joy, peace and perspective about what matters.

Abstract

Objective: To systematically review and evaluate the evidence regarding the efficacy of medications used for procedural sedation (PS) in children requiring emergency procedures.

Methods: Using comprehensive search techniques to avoid selection bias, randomized controlled trials (RCTs) were identified. Trial quality was assessed and efficacy, times and safety of the sedatives were recorded. Quantitative and qualitative summary methods were used.

Results: The 35 included RCTs were of variable quality, and compared a great variety of medications on many different outcomes. Separately or combined, these trials did not demonstrate one particular drug or combination of drugs to be the most effective, timely, or safe.

Conclusions: The ideal PS agent to be used depends on the procedure to be performed and whether or not it will be painful, the duration of sedation required and characteristics of the child involved. Further research is proposed to the compare efficacy, times and safety of different agents.

Acknowledgements

I could never have completed this project without the invaluable time and energy of many people. It is with heartfelt appreciation that I thank the following people who helped bring this work to it's conclusion:

I must first thank Dr. Brian Rowe, my thesis supervisor and mentor. I have learned so much from the many lessons that you very patiently taught me and opportunities you presented me with.

Thank-you to the other members of my thesis committee for their expert help in research methodology as well as writing style, statistics, and common sense:
Dr. Terry Klassen
Lisa Hartling

Thank-you to Natasha Wiebe, for providing patient guidance and recommendations on the statistical aspects of the systematic review.

Thank-you also to Martin V. Pusic for guiding me to begin this degree in the first place. I also wish to acknowledge Dr. Eileen Klein for providing additional data as well as aiding in data extraction, and Kelly Russell for helping on several levels.

Thank-you to the following authors who provided additional data or clarification when possible: Dr. JH Burton, Dr. DM Fatovich, Dr. S Green, Dr. CJ Havel, Dr. RM Kennedy, Dr. TS Sherwin, Dr. MC Theroux, Dr. J Wathen, Dr. P Younge and Mr. N Zoltie.

Finally, I thank the Children's Health Foundation of Northern Alberta, and Departments of Pediatrics and Emergency Medicine at the University of Alberta for the financial support.

Table of Contents

Chapter one: Background 1

Section 1.1: Overview of procedural sedation 1

1.1.1 Introduction 1
1.1.2 Definition of procedural sedation 2
1.1.3 The need for procedural sedation 2
1.1.4 Procedures requiring sedation 3
1.1.5 The Emergency Department setting 3
1.1.6 Medications used for procedural sedation 4

Section 1.2: Preparation for procedural sedation 4

1.2.1 Pre-sedation assessment 4
1.2.2 Monitoring and Equipment 5

Section 1.3: The Ideal agent 5

Section 1.4: Routes of administration of sedative/analgesics 6

1.4.1 Oral (PO)/Rectal (PR) 6
1.4.2 Intranasal (IN) 6
1.4.3 Intramuscular (IM) 7
1.4.4 Intravenous (IV) 7

Section 1.5: Agents (Table 1.4) 7

1.5.1 Sedative-Hypnotics 7
1.5.1.1 Barbiturates 7
1.5.1.2 Benzodiazepines 8
1.5.1.3 Chloral Hydrate 8
1.5.1.4 Propofol (2,6 di-isopropylphenol) 9
1.5.1.5 Etomidate 9
1.5.2 Analgesics 9
1.5.2.1 Opioids 9
1.5.3 Sedative and analgesic combinations 10
1.5.3.1 Meperidine, Promethazine, Chlorpromazine (MPC) 11
1.5.3.2 Fentanyl and midazolam 11
1.5.3.3 Ketamine 11
1.5.3.4 Nitrous oxide (N_2O) 12
1.5.4 Summary of agents 12

Section 1.6: Reversal agents (Table 1.5) 13

Section 1.7: Evaluating sedation and analgesia 13

Section 1.8: Post-sedation monitoring & discharge criteria (Table 1.6) 14

Section 1.9: The Thesis approach 14

Section 1.10: Summary 15

Tables 17

Table 1.1: ASA continuum of sedation(10): 17
Table 1.2: ASA physical status classification system (11) 17
Table 1.3. AAP/ASA guidelines for pre-procedural fasting for elective procedures (9) 18
Table 1.4: Medications used for procedural sedation. 19
Table 1.5: Reversal Agents. 20
Table 1.6: Sample discharge instructions after sedation/analgesia 21

Figures 22
Figure 1.1: Mallampati classification (38) 22

Reference List for Chapter 1 23

Chapter Two: Methods of review and quality of included studies 29

Section 2.1: Introduction 29

Section 2.2: Methods of the review 29
2.2.1 Criteria for including studies in the review 30
2.2.1.1 Study Populations 30
2.2.1.2 Interventions 30
2.2.1.3 Outcome measures 30
2.2.1.4 Types of studies 30
2.2.2 Search strategy 30
2.2.3 Study Identification 31
2.2.4 Quality Assessment of Included Studies (Appendix 2.3) 31
2.2.5 Data Extraction 32
2.2.6 Data Analysis 32

Section 2.3: Results of search 32
2.3.1 Numbers of studies found (Figure 2.6) 32
2.3.2 Characteristics of excluded studies 32
2.3.3 Characteristics of included studies 33
2.3.3.1 Populations evaluated 33
2.3.3.2 Interventions that were compared (Table 2.1) 33
2.3.3.3 Outcome measures used 33

Section 2.4: Methodological quality of the included trials 34
2.4.1 Jadad score (Table 2.4) 34
2.4.2 Allocation concealment (Figure 2.1) 35
2.4.3 QoCoA (Figure 2.2) 35
2.4.4 Agreement of the different quality rating systems 35
2.4.5 Sponsorship 36

Section 2.5: Discussion 36
2.5.1 Deficiencies in allocation concealment 37
2.5.2 Deficiencies in randomization 37
2.5.3 Deficiencies in blinding 37
2.5.4 Overall interpretation 38

Section 2.6: Summary 38

Tables 40

Table 2.1: Number of studies comparing different types of sedatives 40

Table 2.2: Different agents compared with benzodiazepines 40

Table 2.3: Quality scores 41

Table 2.4: Jadad Scores of Included 35 Randomized Controlled Trials 43

Figures 44

Figure 2.1: Allocation Concealment Scores 44

Figure 2.2: Quality of Concealment of Allocation Scores 45

Figure 2.3: Jadad scores of 26 studies that scored greater than 6/10 on Quality of Concealment of Allocation 46

Figure 2.4: Jadad scores of 9 studies that scored less than 7/10 on Quality of Concealment of Allocation 47

Figure 2.5: QUORUM flow chart of retrieved articles (34) 48

Reference List for Chapter 2 49

Chapter Three: Summary of results of systematic review 54

Section 3.1: Introduction to results of systematic review 54

3.1.1 Summary of search and selection of studies 54

3.1.2 Methods of Data Analysis 54

Section 3.2: Quantitative Results 55

3.2.1 Oral benzodiazepines vs. placebo (t=3, n=195) 55

3.2.2 IV Ketamine with and without midazolam (t=2, n=370) 56

3.2.3 Nitrous oxide (N_2O) vs. placebo (oxygen) (t=2, n=51) 56

Section 3.3: Qualitative Results 56

3.3.1 Opiates vs. other agents (t=8, n=627; 1 trial (n=42) used in both sections) 57

3.3.1.1 Opiates vs. meperidine, promethazine and chlorpromazine (MPC) (t=3, n=123) 57

3.3.1.2 Opiates plus another sedative agent vs. other agents (t=6, n=546) 57

3.3.2 Ketamine vs. other agents (t=11, n=1137) 57

3.3.2.1 Ketamine vs. benzodiazepines (t=4, n=482) 57

3.3.2.2 Ketamine vs. other agents (t=7, n=655) 57

3.3.3 MPC vs. other sedatives (t=6, n=266) 58

3.3.4 Benzodiazepines vs. other agents (t=25, n=2140) 58

3.3.4.1 Benzodiazepines vs. placebo or standard care (t=6, n=492) 58

3.3.4.2 Benzodiazepines vs. benzodiazepines (t=4, n=298) 58

3.3.4.3 Benzodiazepines vs. other agents (t=8, n=702) 59

3.3.4.4 Benzodiazepines combined with other sedatives or analgesics (t=7, n=648) 59

3.3.5 N_2O vs. other agents (t=4, n=370) 59

3.3.6 Barbiturates vs. other agents (t=3, n=141) 60

3.3.7 Propofol vs. other agents (t=2, n=202) 60
3.3.8 Etomidate vs. other agents (t=3, n=133) 60

Section 3.4: Adverse Effects **60**
3.4.1 Frequency of adverse effects 60
3.4.2 Types of adverse effects reported 60
3.4.3 Adverse effects with opiates 61
3.4.4 Adverse effects with ketamine 61
3.4.5 Adverse effects with MPC 62
3.4.6 Adverse effects with benzodiazepines 62
3.4.7 Adverse effects with N_2O 62
3.4.8 Adverse effects with barbiturates 62
3.4.9 Adverse effects with propofol 63
3.4.10 Adverse effects with etomidate 63

Section 3.5: Discussion **63**
3.5.1 Quantitative analysis 63
3.5.2 Qualitative analysis 64
3.5.2.1 The most efficacious medication 64
3.5.2.2 The sedation regimen with the fastest times 64
3.5.2.3 Sedating with the fewest adverse effects 65

Section 3.6: Summary **67**

Tables **68**
Table 3.1: Outcomes of PO benzodiazepines vs. placebo 68
Table 3.2: Outcomes of IV Ketamine with and without midazolam 68
Table 3.3: Outcomes of nitrous oxide (N_2O) vs. placebo 69
Table 3.4: Outcomes of opiates vs. meperidine, promethazine and chlorpromazine (MPC) 69
Table 3.5: Outcomes of opiates vs. other agents 70
Table 3.6: Outcomes of ketamine vs. benzodiazepines 71
Table 3.7: Outcomes of ketamine vs. other agents 72
Table 3.8: Outcomes of meperidine, promethazine and chlorpromazine (MPC) vs. other agents 73
Table 3.9: Outcomes of benzodiazepines vs. placebo or standard care 74
Table 3.10: Outcomes of benzodiazepines vs. benzodiazepines 75
Table 3.11: Outcomes of benzodiazepines vs. other agents 76
Table 3.12: Outcomes of benzodiazepine plus another agent vs. other agents 78
Table 3.13: Outcomes of nitrous oxide (N_2O) vs. other agents 79
Table 3.14: Outcomes of barbiturates vs. other agents 80
Table 3.15: Outcomes of propofol vs. other agents 81
Table 3.16: Outcomes of etomidate vs. other agents 82
Table 3.17: Types of times studied in randomized control trials (RCTs) 83
Table 3.18: Adverse effects (AE) with opiates 86
Table 3.19: Adverse effects (AE) with ketamine 87

Table 3.20: Adverse effects (AE) with benzodiazepines 88
Table 3.21: Adverse effects (AE) with N_2O 89
Table 3.22: Adverse effects (AE) with barbiturates 89
Table 3.23: Adverse effects (AE) with propofol 89
Table 3.24: Adverse effects (AE) with etomidate 90

Figures 91
Figure 3.1: Metaview of benzodiazepines vs. other sedatives 91
Figure 3.2: Metaview of nitrous oxide (N_2O) vs. other sedatives 91
Figure 3.3: Graph of times to discharge by different sedatives 92
Figure 3.4: Percentage (%) of adverse effects that occurred 93

Reference List for Chapter 3 94

Chapter Four: Future directions 98

Section 4.1: Introduction to future directions 98

Section 4.2: Survey 98

Section 4.3: The Chart Review 100

Section 4.4: Randomized controlled trials 100
4.4.1 Population 101
4.4.2 Intervention 101
4.4.3 Outcome measures 102
4.4.4 Design 103
4.4.5 Advantages and disadvantages of a multi-centre trial 103
4.4.6 Funding 104

Section 4.5: Clinical Practice Guidelines 104
4.5.1 Rationale 104
4.5.2 Consensus development 105
4.5.3 Monitoring forms 105
4.5.4 Outcome studies 106

Section 4.6: Summary 106

Table 107
Table 4.1 Children's Hospital of Wisconsin Sedation Scale (17) 107

Figure 108
Figure 4.1: Process for creating Clinical Practice Guidelines 108

Reference List for Chapter 4 109

Appendices 111

Appendix 2.1: Search Strategy 111

Appendix 2.2: Relevance form for inclusion (2 pages) 112

Appendix 2.3: Jadad Score, Allocation Concealment Score, and Quality of Concealment of Allocation (3 pages)....114

Appendix 2.4: Data Extraction form *(9 pages)*....117

Appendix 3.1: Children's Hospital of Eastern Ontario Pain Score (CHEOPS) (7)....125

Appendix 3.2: Observational Score of Behavioral Distress Revised.....126

Appendix 3.3: Ramsay Sedation Score (8)....127

Reference List for Appendices....128

List of Tables

Table 1.1: ASA continuum of sedation....17
Table 1.2: ASA physical status classification system....17
Table 1.3. AAP/ASA guidelines for pre-procedural fasting for elective procedures....18
Table 1.4: Medications used for procedural sedation....19
Table 1.5: Reversal Agents....20
Table 1.6: Sample discharge instructions after sedation/analgesia....21

Table 2.1: Number of studies comparing different types of sedatives....40
Table 2.2: Different agents compared with benzodiazepines....40
Table 2.3: Quality scores....41
Table 2.4: Jadad Scores of Included 35 Randomized Controlled Trials....43

Table 3.1: Outcomes of PO benzodiazepines vs. placebo....68
Table 3.2: Outcomes of IV Ketamine with and without midazolam....68
Table 3.3: Outcomes of nitrous oxide (N_2O) vs. placebo....69
Table 3.4: Outcomes of opiates vs. meperidine, promethazine and chlorpromazine (MPC)....69
Table 3.5: Outcomes of opiates vs. other agents....70
Table 3.6: Outcomes of ketamine vs. benzodiazepines....71
Table 3.7: Outcomes of ketamine vs. other agents....72
Table 3.8: Outcomes of meperidine, promethazine and chlorpromazine (MPC) vs. other agents....73
Table 3.9: Outcomes of benzodiazepines vs. placebo or standard care....74
Table 3.10: Outcomes of benzodiazepines vs. benzodiazepines....75
Table 3.11: Outcomes of benzodiazepines vs. other agents....76
Table 3.12: Outcomes of benzodiazepine plus another agent vs. other agents....78
Table 3.13: Outcomes of nitrous oxide (N_2O) vs. other agents....79
Table 3.14: Outcomes of barbiturates vs. other agents....80
Table 3.15: Outcomes of propofol vs. other agents....81
Table 3.16: Outcomes of etomidate vs. other agents....82
Table 3.17: Types of times studied in randomized control trials (RCTs)....83
Table 3.18: Adverse effects (AE) with opiates....86
Table 3.19: Adverse effects (AE) with ketamine....87
Table 3.20: Adverse effects (AE) with benzodiazepines....88
Table 3.21: Adverse effects (AE) with N_2O....89
Table 3.22: Adverse effects (AE) with barbiturates....89
Table 3.23: Adverse effects (AE) with propofol....89
Table 3.24: Adverse effects (AE) with etomidate....90

Table 4.1 Children's Hospital of Wisconsin Sedation Scale....107

List of Figures

Figure 1.1: Mallampati classification 22

Figure 2.1: Allocation Concealment Scores 44
Figure 2.2: Quality of Concealment of Allocation Scores 45
Figure 2.3: Jadad scores of 26 studies that scored greater than 6/10 on Quality of Concealment of Allocation 46
Figure 2.4: Jadad scores of 9 studies that scored less than 7/10 on Quality of Concealment of Allocation 47
Figure 2.5: QUORUM flow chart of retrieved articles 48

Figure 3.1: Metaview of benzodiazepines vs. other sedatives 91
Figure 3.2: Metaview of nitrous oxide (N_2O) vs. other sedatives....................91
Figure 3.3: Graph of times to discharge by different sedatives 92
Figure 3.4: Percentage (%) of adverse effects that occurred 93

Figure 4.1: Process for creating Clinical Practice Guidelines....................108

List of Symbols, Nomenclature, or Abbreviations

χ2	Chi-square statistic
%	Percent
>	Greater than
<	Less than
ASA	American Society of Anesthesiologists
AAP	American Academy of Pediatrics
ACEP	American College of Emergency Physicians
AHFMR	Alberta Heritage Foundation for Medical Research
BP	Blood pressure
CAEP	Canadian Association of Emergency Physicians
CARG	Cochrane Anaesthesia Review Group
CENTRAL	Cochrane Central Register of Controlled Trials
CHEOPS	Children's Hospital of Eastern Ontario Pain Score
CI	Confidence interval
CPGs	Clinical practice guidelines
CT	Computed tomography
ECG	Electrocardiogram
e.g.	for example; latin: exemplum gratii
EMBASE	Excerpta Medica database
ET	Endotracheal
Etc	etcetera
ED	Emergency department
EP	Emergency Physician
GABA	Gamma-aminobutyric acid
ICP	Intra-cranial pressure
i.e.	id est; that is
I^2	I-squared
IM	Intramuscular
IN	Intranasal
IV	Intravenous
kg	Kilogram
mcg	Microgram
MD	Mean difference
MEDLINE	MEDlars onLINE
mg	Milligram
MPC	Meperidine, promethazine, chlorpromazine
MRI	Magnetic resonance imaging
NA	North America
N_2O	Nitrous oxide
NS	Not significant
OR	Operating room
OR	Odds ratio

OSBD/R	Observational scale of behavioural distress/revised
PED	Paediatric emergency department
PERC	Paediatric Emergency Research of Canada
PO	Per os
PR	Per rectum
Q	Every
RCT	Randomized controlled trial
RD	Risk difference
RR	Risk ratio
SC	Subcutaneous
TM	Transmucosal
vs.	Versus
USA	United States of America
VAS	Visual analog scale
WMD	Weighted mean difference

Chapter one: Background

Section 1.1: Overview of procedural sedation

1.1.1 Introduction

Children often require sedation for brief procedures in the emergency department (ED) that are painful, anxiety provoking, or both. For example, they may have a fractured bone that needs reduction, a laceration that requires repair or require a computed tomography (CT) scan that requires them to lie perfectly still. The subjective nature of pain and anxiety makes these phenomena difficult to evaluate in children, and care providers often struggle to identify the appropriate analgesia and sedatives.(1)

There are non-pharmacological measures as well as many medications that may be used for the purpose of completing painful and/or anxiety provoking procedures, with a great variety of effect and complications. Several techniques have been used to reduce anxiety and the perception of pain in children, including hypnosis, distraction, visual imagery, and simple explanation and preparation of the child. While these methods are useful for short, less-painful procedures and as adjuncts, many emergency procedures in children are too painful or anxiety provoking to be tolerated without pharmacological influence. Moreover, many ED physicians are not familiar with such techniques (e.g. hypnosis), so their application is limited.

Considerable controversy has arisen regarding the topic of which medications are appropriate for use outside of the operating room.(26;52;56) Several guidelines and official statements have been created to attempt to address this issue.(5-10;33;37)

The approach used until recently was: 1) operative referral (and the side effects and complications associated with this approach); 2) heavy sedation (and the associated complications and side effects); or 3) "brutane", that is using physical restraint techniques to complete the procedure without any or minimal sedation or analgesia. The current approach in most North American (NA) EDs and Paediatric Emergency Department (PED) settings is procedural sedation.

This thesis involved a systematic review to identify and explore the literature regarding "Options for procedural sedation in paediatric patients requiring painful or anxiety provoking procedures in Emergency Departments". The thesis proposes future directions including a survey and chart review of current practice in this area, followed by a randomized controlled trial of the agents deemed most efficacious in the systematic review. It also explored the potential design of a clinical practice guideline (CPG).

1.1.2 Definition of procedural sedation

Previously "conscious sedation" was defined by the American Academy of Pediatrics (AAP)(6) as "a medically controlled state of depressed consciousness that (1) allows protective reflexes to be maintained; (2) retains the patient's ability to maintain a patent airway independently and continuously; and (3) permits appropriate response by the patient to physical stimulation or verbal command, e.g. 'open your eyes'". This term has been confusing, as often the patients are not conscious, requiring deeper sedation in order to perform the procedure. This is challenging to achieve consistently, as it is impossible to predict with certainty how an individual patient will respond to each medication. The AAP Committee on Drugs recommends that it is more appropriate to recognize the most current terminology of the American Society of Anesthesiologists (ASA) and replacement of the term "conscious sedation" with "moderate sedation." Others have suggested the term "procedural sedation".

Guidelines from the ASA(10) include a definition of the continuum of sedation that occurs when sedative and analgesic medications are administered (see Table 1.1). Procedural sedation is defined by the American College of Emergency Physicians (ACEP) as: "A technique of administering sedatives or dissociative agents with or without analgesics to induce a state that allows the patient to tolerate unpleasant procedures while maintaining adequate cardio-respiratory function. Procedural sedation and analgesia is intended to result in a depressed level of consciousness but one that allows the patient to maintain airway control independently and continuously. Specifically, the drugs, doses and techniques used are not likely to produce a loss of protective airway reflexes".(8) Procedural sedation is the term most commonly used in EDs in NA.

1.1.3 The need for procedural sedation

Oligo-analgesia (inadequate pain control) and insufficient sedation are concepts that are emerging in the Emergency Medicine literature and becoming less acceptable to emergency physicians, nurses, patients and their families. Compared with adults, children receive less medication per kilogram for pain.(20) Without adequate procedural sedation, children experience unnecessary pain and/or distress. Parents and healthcare professionals have anxiety of their own. A suffering child is also an uncooperative patient, which impairs control over the procedure, making it difficult to successfully complete.(48;54;57;59)

Given the issues of oligo-analgesia, parental and patient distress, and poorer outcomes, many EDs are moving to the adoption of procedural sedation guidelines for patients requiring painful or anxiety provoking procedures. Choosing appropriate sedation for procedures is a serious decision that confronts Emergency Physicians (EPs) on a daily basis.

Reasons for this common problem include a lack of consensus on the best medication, dose, and route of administration for procedures. Other obstacles to the use of procedural sedation include lack of agreement on monitoring, lack of familiarity with children, lack of training in procedural sedation techniques, and a fear of adverse effects. Another problem some physicians encounter when faced with the choice of sedating a child in the ED is that their anaesthesia colleagues discourage procedural sedation. This is a topic of controversy that has been widely debated in the literature. The EP's point of view is that they are well trained in using the drugs and comfortable managing the possible adverse events that may arise. Anaesthetists feel that this is something best reserved for the ideally controlled setting of the operating theatres. Unfortunately, there is not enough manpower and operating rooms to accommodate doing most of these procedures. On a positive note, EPs have had more training and experience in this area than ever before, and can safely perform this practice.(33;52)

1.1.4 Procedures requiring sedation

Procedures that frequently require procedural sedation include laceration repair; fractures or dislocation reduction; burn dressings; wound debridement and repair; abscess drainage; and arthrocentesis. Other situations in which sedation should be considered are when performing lumbar puncture; bone marrow aspiration; foreign body removal; eye examination; gynaecologic examination; hernia reduction; testicular detorsion and paraphimosis reduction. Less common procedures include removal of foreskin caught in zipper; rectal prolapse reduction; dental procedures and manual disimpaction of stool. Diagnostic imaging such as CT; magnetic resonance imagine (MRI) or ultrasound as well as resuscitation measures including central venous line placement; chest tube placement and cardioversion also may benefit from pharmacological restraint.

1.1.5 The Emergency Department setting

The ED is a unique setting in which large volumes of patients are seen 24 hours a day, seven days a week. Physicians and nurses have a variety of skill levels and expertise, and patients present with a wide spectrum of acuity and severity, as well as a variety of diagnoses that span the entire field of medicine. The environment is often chaotic, and there is limited continuity of care as a result of shift work.

Procedures performed in the ED are associated with different challenges than occur for elective cases. For example, acute and unexpected injury, concurrent or co-morbid illness, presence of stomach contents, noisy environment, and limited preparation time all make these procedures potentially more risky. Additional distinctions include variable levels of available monitoring (there is less than in the operating room (OR); however, there is more than in outpatient settings such as dental offices), as well as the availability of allied health professionals for assistance, such as respiratory therapists (there are more in the ORs and less in outpatient clinics, compared with EDs). Another unique characteristic of many procedures performed in the ED is the relatively short nature.

1.1.6 Medications used for procedural sedation

Medications that have been used for these procedures include classes such as sedative/hypnotics (midazolam, diazepam, lorazepam, chloral hydrate, propofol, etomidate)(36;40), narcotics (fentanyl, morphine, meperidine)(12;49), inhalation agents (nitrous oxide)(23) and dissociative agents (ketamine).(27;29) There are different routes by which to administer these agents, including transmucosally (TM), orally (PO), rectally (PR), intravenously (IV), intramuscularly (IM), intranasally (IN), and inhalationally. There is great variety in the degree of efficacy of sedation provided by each of these classes and routes of drugs, as well as variability of their safety profiles.(19)

Section 1.2: Preparation for procedural sedation

1.2.1 Pre-sedation assessment

An appropriate history and focused physical exam should be performed prior to initiating procedural sedation. Allergies (or prior problems with anaesthetics), medications, past medical history, time of last solid and liquid intake, and events leading to the need for sedation are important to ascertain. Examination should focus attention to the upper airway (the Mallampati classification(37): Figure 1.1, dental devices, mandible size, neck size and flexion) and breathing in preparation for intubation in the event of respiratory depression by the medications. Signs of perfusion, including blood pressure and the patient's level of consciousness should be evaluated before beginning sedation, as this will impact the choice of sedative used. Awareness of any potential compromise to these areas of basic life support will ensure the team is ready for any possible complications that may arise.

Anaesthesia should be consulted and consideration be given to performing the procedure in the operating room for patients with an ASA classification of 3 or greater (Table 1.2). Patients with severe systemic disease will be at greater risk of adverse outcomes and therefore would be best sedated in a controlled environment (the OR) with all precautions taken.

Fasting guidelines for healthy patients undergoing elective procedures may not be appropriate in emergency situations. Brady (16) published a systematic review in the Cochrane Library with the conclusion that "there was no evidence to suggest that a shortened fast results in an increased risk of aspiration, regurgitation or related morbidity" in adults. These authors are reviewing the same topic in children, the results of which are pending.(16)

Agrawal (4) performed a prospective case series to record the pre-procedural fasting state and adverse events that occurred in 905 of 1014 children who underwent procedural sedation in the ED during an 11-month period. These investigators found that more than half of the patients did not meet the fasting guidelines (Table 1.3) and there was no difference between fasted and non-fasted children in airway complications, emesis or other adverse events. In 1997, Ingebo et al concluded that there is no advantage in requiring children to fast for longer than two hours after clear liquid ingestion before sedation or anaesthesia for any procedure.(32) Ghaffar et al demonstrated no difference in the rate of vomiting between short (less than two hours) and long (greater than two hours) fasting times.(24)

1.2.2 Monitoring and Equipment

Depending on the depth of sedation desired and the setting, different levels of monitoring should be instituted. According to the Canadian Association of Emergency Physicians (CAEP) Consensus Guidelines for Procedural Sedation and Analgesia(33), aside from the person performing the procedure, one health care worker who is trained in sedation and skilled in airway management should be designated to manage the medications as well as their possible adverse effects. In the peripheral centres, this may not be practically feasible. For this reason, clinicians must balance the risks and benefits of performing that procedure under sedation and make a judgement call that incorporates choosing the type of medication(s) used.

An oxygen delivery system, oral airway, and bag-valve-mask should be available at the bedside because most sedatives have some risk of respiratory depression. An intravenous line may be placed at the physician's discretion; however, some agents may be delivered through other routes, so this is not always required. A cardiac arrest cart with standard medications for resuscitation should be nearby in the event of rare but potentially devastating complications resulting in cardio-pulmonary arrest. Exhaled carbon dioxide levels may also be useful, if available. Monitoring should include pulse oximetry for light sedation, as well as continuous electrocardiograph (ECG) and intermittent blood pressure (BP) monitoring for deeper sedation. Vital signs should be recorded at baseline, after each dose of medication, every five minutes during deep sedation, at the end of the procedure, during recovery, and at discharge. A standard procedural sedation record should be used.

Section 1.3: The Ideal agent

The ideal agent for procedural sedation would:

1. Have a rapid onset and recovery time;

2. Be titratable (i.e.: allow administration of small amounts of medication to gradually adjust the depth of sedation so as to achieve the level required to perform the procedure while minimizing adverse events);
3. Be consistently efficacious in achieving loss of consciousness and amnesia with or without analgesia while maintaining cardiopulmonary homeostasis;
4. Be painless to administer;
5. Cause no significant adverse effects;
6. Be easy to reverse; and,
7. Allow motor control of the patient.

Although many pharmaceutical agents have some of these qualities to varying degrees, none optimally achieve all of them.

In conducting the thorough and systematic search (see Chapter 2) for relevant studies on this topic, no reports were found of the epidemiology of what physicians are using for the purpose of procedural sedation across Canada, North America or internationally. This reflects the lack of consensus on this important topic, as each centre searches for the appropriate agent for their setting. It also reflects the fact that one agent or combination may be ideal in one setting, such as a large hospital ED in a major city, but not appropriate in another, such as a remote ED that is not staffed with respiratory technicians and afforded the luxuries that tertiary care centres have.

Section 1.4: Routes of administration of sedative/analgesics

There are five routes for administration of sedative/analgesics to children, each with advantages and disadvantages.

1.4.1 Oral (PO)/Rectal (PR)

Giving drugs orally and rectally are popular choices because both are relatively easy routes that do not distress most patients. However, these routes have an unpredictable, prolonged onset of action and an unacceptably protracted recovery time. They have variable absorption and levels of sedation, thus delaying ED procedure times and providing inadequate levels of anaesthesia. These approaches remain infrequently used in most NA EDs.

1.4.2 Intranasal (IN)

Some researchers have advocated administering drugs intranasally because of absorption across richly vascularized mucosa with direct transport of the medication into the systemic circulation. This avoids first pass metabolism and may increase bioavailability. Some physicians(28) believe there is high patient acceptability compared with rectal, intramuscular or intravenous methods. Disadvantages include variable absorption (with potential for prolonged onset and offset of action), variable levels of sedation and irritation on administration. These problems render intranasal medications unsuitable for many procedures attempted/performed/completed in emergency departments and they remain infrequently used in most NA EDs.

1.4.3 Intramuscular (IM)

Intramuscular injection is a painful route that cannot be titrated, and the onset of the resulting sedation is erratic. However, agents such as ketamine have been successfully used as an intra-muscular procedural sedation for some time.(27)

1.4.4 Intravenous (IV)

The IV approach is most commonly employed. The main drawbacks are that it is painful, particularly if multiple attempts are required, and there is a remote risk of introducing infection. The benefits include direct delivery to the systemic system, which affords rapid and reliable onset and duration of effect. It allows IV access in case of need for:

1. Drug titration;
2. A reversal agent;
3. Other medications;
4. Fluid.

For most emergency procedures that require sedation and analgesia, IV access is not only warranted, but the ideal route.

Section 1.5: Agents (Table 1.4)

The following sections outline the range of medications available for procedural sedation and attempt to examine literature related to their use in children. In 1992, chloral hydrate was the most common drug used for sedation; a combination of parenteral meperidine, promethazine, and chlorpromazine, was the second; and pentobarbital the third.(18) Today, there is a great variety in the choices being made, with the traditional benzodiazepines (with or without opiates) being used more frequently as well as propofol and etomidate. Ketamine has made a resurgence in the ED, as well, for use in these situations.

1.5.1 Sedative-Hypnotics

1.5.1.1 Barbiturates

Barbiturates are one of the oldest classes of agents used for sedation and act at numerous sites in the central nervous system. They depress the reticular activating system as well as the medullary ventilatory centres, causing hypoventilation and apnoea. Respiratory reflexes are usually not depressed and can be heightened, potentially causing laryngospasm.

These sedative-hypnotics have been largely replaced in the ED setting by more advanced agents; however they remain a typical choice for patients with suspected increased intra-cranial pressure (ICP). Barbiturates have no analgesic properties, and therefore are useful for non-painful, but anxiety provoking procedures (such as diagnostic imaging). However, if analgesia is required, they must be combined with another agent. Side effects include rate and dose dependent laryngospasm, bronchospasm, cough, respiratory suppression, myocardial depression and hypotension. They are contra-indicated in patients with porphyria, a rare hemoglobinopathy.

Commonly used barbiturates for procedural sedation include pentobarbital, thiopental and methohexital. Methohexital and thiopental are ultrashort-acting barbiturates (i.e. onset within 60 seconds when given intravenously). One study reported only a two percent side-effect rate with 25 to 50 mg/kg of rectal thiopental in over 1000 patients.(42) Pentobarbital has been the most widely used of the barbiturates for paediatric procedural sedation.(18)

1.5.1.2 Benzodiazepines

As the most commonly used sedative-hypnotics, these agents have anxiolytic, amnestic, and skeletal muscle relaxant properties but no analgesic effects. They act on the benzodiazepine receptors to potentiate the inhibitory action of the neurotransmitter gamma-aminobutyric acid (GABA). By increasing the influx of chloride ions into the cell, GABA inhibits the ability to initiate an action potential.

Agents in this class include diazepam, lorazepam and most commonly, midazolam. Midazolam has largely replaced diazepam as an agent for use in procedural sedation. Although diazepam can be an effective drug, midazolam has a quicker onset of sedation and patients recover more rapidly. There is also greater reported amnesia and less burning pain on injection with midazolam.(62)

As benzodiazepines have no analgesic effect they are often used in conjunction with narcotics, which may exacerbate the associated risks of respiratory depression and hypotension. Paradoxical excitation or hyper-agitation can occur in some children, a particular challenge in children requiring a procedure for which they need to be relatively still. Contra-indications include hypersensitivity, acute narrow and/or open angle glaucoma, myasthenia gravis, and hepatic or renal dysfunction.

1.5.1.3 Chloral Hydrate

This sedative-hypnotic is historically one of the most commonly used agents for imaging, and one that has been popular in the past for procedural sedation.(14)

Its action occurs when it is irreversibly converted to trichloroethanol, but the exact mechanism of action for chloral hydrate is unknown. It is an agent that takes up to one hour to have its effect, can last for hours, and has associated risks including aspiration, respiratory depression, arrhythmias, and death, making it unsatisfactory for ED use.(44)

1.5.1.4 Propofol (2,6 di-isopropylphenol)

This non-opioid, non-barbiturate sedative-hypnotic is becoming a popular choice for brief procedures in children in emergency settings.(25) Like many other drugs in this class, propofol mediates activity of the GABA receptors. It has anti-convulsant properties, amnestic effect, and lowers intra-cranial pressure. It may, however, cause apnoea, hypotension, and reduced cardiac output (in all patients, irrespective of the presence or absence of cardiac disease), and should be used only by physicians who are comfortable managing these potential complications. Infusions must only be used on a short-term basis (less than several hours), as long-term use has been associated with serious adverse events. Health Canada has stated that: "Propofol is contraindicated for the sedation of children 18 years or younger receiving intensive care"; however, its use appears to be increasing in children. Propofol lacks analgesic effect, and is commonly combined with an opioid such as fentanyl. Propofol has been found to "burn" with injection; this can be avoided by injecting up to one millilitre of 1% lidocaine before or with it.(43) Propofol is contraindicated in patients with egg or soybean allergy, known hypersensitivity or disordered fat metabolism.

1.5.1.5 Etomidate

An imidazole derivative, etomidate has been recently demonstrated to be a useful sedative in many emergency procedures.(31;46) It appears to act like GABA and exerts its action by depressing the activity of the brain stem reticular activating system. Its lack of clinically significant hemodynamic alterations and its minimal side effects give rise to interest in exploring this agent for use in procedural sedation. While etomidate is known to cause suppression of the adrenal gland, these effects are transient and thought to have little if any clinical consequence. Not currently available in Canada except in special circumstances, etomidate has been used successfully for years in the USA.

1.5.2 Analgesics

1.5.2.1 Opioids

Derived from a sap taken from a seedpod of the plant "papaver somniferum", the opioids are a class of drugs that includes morphine, fentanyl, meperidine and diamorphine (available in Europe but not Canada). These medications are the most common choices for analgesia in the emergency setting and elsewhere. One study evaluated 2,828 patients with isolated closed fractures of the extremities or clavicle, and found that 64% received any analgesic and 42% received a narcotic analgesic.(17) This medication class continues to be the gold standard for acute pain control and controls pain by inhibition of neurotransmitter release from the primary afferent terminals in the spinal cord and activation of descending inhibitory controls in the midbrain.

Hemodynamic compromise and pruritis are histamine induced adverse effects that occur to a greater degree with morphine than with synthetic fentanyl. Rapidly administered large doses of fentanyl (usually >5mcg/kg) may cause chest wall rigidity. Naloxone can reverse many of the adverse effects of narcotics, but chest wall rigidity may necessitate paralysis and intubation. Narcotics are contra-indicated in patients with hypersensitivity and severe respiratory depression.

Morphine is the classic opioid analgesic. It has minimal cardiovascular effects but can cause the release of histamine, which results in peripheral venous and arteriolar dilation, potentially causing decreased blood pressure in patients who are relatively hypovolemic. On occasion, morphine can increase vagal tone, leading to a decrease in heart rate.

Fentanyl is a synthetic opioid that has a rapid onset and short duration, is reversible, and is 50-100 times more potent than morphine. It is the most commonly used opioid in the ED.(44) The main benefit over other narcotics is the comparatively minimal histamine release, and limited cardiovascular side effects. It has been incorporated into a lollipop that is non-threatening and easy to administer to children. This form has been found to cause significant vomiting and pruritis, however, and is not recommended for procedural sedation.(44)

Meperidine is a synthetic narcotic analgesic that has limited use in EDs. If given IM or subcutaneously (SC), meperidine is irritating to tissues and incompletely and erratically absorbed. Meperidine is metabolized to the active metabolite, normeperidine, which has a half-life of 15 to 20 hours. Normeperidine accumulates, particularly with large repeated doses or decreased renal function, and can cause dysphoria, irritability, tremors, myoclonus, and seizures.(15)

Diamorphine is rapidly and well absorbed (lipophilic), has low irritancy, and has twice the potency of morphine with a similar duration of action. It is not a commonly used medication in NA but is readily available in the United Kingdom.(61)

1.5.3 Sedative and analgesic combinations

Several sedative/analgesic combinations have been developed for use during painful procedures in children. Historically, the most popular "lytic" cocktail was DPT (Demerol (meperidine), Promethazine, Thorazine (chlorpromazine)). In more recent years, fentanyl and midazolam have been combined in an attempt to provide sedation as well as analgesia.(44)

1.5.3.1 Meperidine, Promethazine, Chlorpromazine (MPC)

Prior to February 1954, sodium quinalbarbitone (Seconal) and meperidine were used for sedation at the Hospital for Sick Children in Toronto. Paediatric cardiologists published a landmark article in 1958 introducing a "Catheter Mixture" that included meperidine along with chlorpromazine and promethazine.(51) They found this cocktail to provide good sedation and analgesia to 670 children undergoing cardiac catheterization. It has the added benefit of being anti-emetic. Smith et al reported lip smacking in many patients, with temporary drops in blood pressure in some patients and depressed breathing in one patient. Only one patient died as a result of receiving the sedation mixture, a gravely ill, cyanotic two month old infant.(51)

However, this concoction has a delayed onset of action, can last up to several hours, has a high failure rate for sedation in paediatrics, and carries a risk of respiratory depression/arrest at even less-than-recommended doses. Moreover, it can cause potential dystonic reactions in many patients. For these many reasons, this triad is no longer recommended(13;15;55) and is infrequently used.

1.5.3.2 Fentanyl and midazolam

In recent years, this combination of agents has become the standard of care for ED procedural sedation.(60) Many emergency physicians combine these two agents to achieve analgesia, sedation, anxiolysis, amnesia, and muscle relaxation. The drawback is a higher incidence of respiratory depression, as the agents are synergistic.

1.5.3.3 Ketamine

A non-barbiturate phencyclidine derivative that provides dissociative sedation, analgesia and amnesia, ketamine is a popular choice for many ED procedures. In some departments, it is the most commonly used medication for this purpose.(41) The mechanism of action is to block activation of non-competitive N-Methyl-D-Aspartate receptors for the excitatory neurotransmitter, glutamate. It has cardio-stimulatory effects, which makes it ideal for patients in whom hemodynamic compromise must be avoided. It may be administered PO, with 16% bioavailability compared with 93% when given IV or IM.

The primary adverse effects of ketamine are "emergence phenomena". These are perceptual disturbances such as alteration in mood, vivid or unpleasant dreams, and hallucinations during or after emergence from sedation. Addition of midazolam may reduce these adverse perceptual effects, although studies have not supported this theory.(50;58)

Ketamine may cause excessive salivation, which may be avoided by pre-treatment with atropine or glycopyrrolate. Laryngospasm and increased systemic, intra-cranial and intra-ocular pressures have also been described effects of ketamine; therefore it is contra-indicated in patients with these conditions.

1.5.3.4 Nitrous oxide (N_2O)

N_2O is a safe and effective sedative/analgesic gas that has been in use since the late 18th century for both surgical and recreational purposes. The mechanism of action is unknown but it has been postulated that it may potentiate the release of inhibitory neurotransmitters to inhibit excitatory synapses.

The only inhalational anaesthetic available to most EDs is N_2O, an agent that provides anxiolysis and mild analgesia. It must be combined with oxygen (usually > 50%), and requires a scavenging system. It is usually self-administered, using a "demand valve", and consequently requires a co-operative patient.

Adverse effects include nausea and vomiting. Another concern is diffusional hypoxia in the recovery phase. As the nitrous oxide is washed out of the system through the lungs, it displaces oxygen and can cause hypoxia. This can be avoided by providing supplemental oxygen throughout the recovery phase. Because of its 32-fold higher solubility coefficient than air, nitrous oxide preferentially enters areas of the body such as the gut and middle ear, possibly leading to over-distension. As such, contraindications to its usage would include conditions exacerbated by gas expansion, such as bowel obstruction, pneumothorax, severe lung disease, procedures using balloon-tipped catheters, and with middle ear effusions.(47)

1.5.4 Summary of agents

Considerable controversy has arisen regarding the topic of which medications are appropriate for use outside of the operating room.(26;52;56) Benzodiazepines can be effective sedatives(56), however, there is a narrow and unpredictable therapeutic window, and they are not useful in isolation for procedures that are painful. In order to achieve adequate analgesia, benzodiazepines must be given in conjunction with other medications that can result in increased complication rates.(47;53) Ketamine has been found to be an excellent dissociative agent and analgesic.(34) Drawbacks exist, however, including some patients and circumstances in which ketamine is contraindicated, such as with increased intra-cranial pressure. There are a few rare adverse effects that may occur with ketamine, including transient apnoea or laryngospasm, and emergence phenomena.(27) Chloral hydrate has a slow onset of action, has no analgesic properties, and is not considered appropriate for painful or anxiety provoking procedures in the ED.(15) Nitrous oxide has been shown to be of some limited use in this setting, but again has a significant adverse event rate that deems it less than ideal.(15) Propofol has recently been found to be an excellent medication for use in procedural sedation(29), however there is relatively little data on its use in children. Etomidate is a promising drug and new research is demonstrating its potential for use in this setting.(31;35;46)

Section 1.6: Reversal agents (Table 1.5)

The situation may arise when serious adverse effects occur and the physician may wish to terminate the effect of the sedative or analgesic. Sedation, analgesia and some of the complications that arise from the use of opiates or benzodiazepines can be reversed. Reversal of sedation or analgesia should be weighed carefully to balance the benefits against the possible risks. Many advocate supportive care while awaiting the respiratory depressant effect to abate.(30) If sedation is reversed, the patient must be observed for at least 2 hours, until the physician is sure that the child will not become re-sedated once the reversal agent has worn off.(30)

Section 1.7: Evaluating sedation and analgesia

Conducting research on procedural sedation requires a valid and clinically relevant outcome measure. Interpreting the depth and quality of sedation is very subjective, and clinicians and investigators have struggled to find a tool that is sensible, valid, reliable and responsive to change.(21;39;45) There are three main categories of outcomes evaluated in research on this topic: 1) efficacy; 2) times of onset, duration of medication etc.; and, 3) adverse event rates. These outcomes have all been evaluated in several different ways. Efficacy has been examined using sedation scores, pain scores, distress scores, anxiety scores, and satisfaction scores (qualitative as well as numeric scales).(21;39;45) Less commonly used outcome measurements include activity scores, tolerance or cooperation scores, and success or ease of procedure. While there is no single score that is superior to the others, each has pros and cons. Some have been validated(45), while others have been shown to be reliable(39) and still others are sensible.(21)

Many studies record onset of sedation or time needed from beginning of drug administration to the start of the procedure, time to complete the procedure, length of sedation, time from administration of study drug until recovery or disposition. There are different advantages to each of these. The sedation time will provide an accurate reflection of the duration of action of the medication being evaluated, but does not take other real-life occurrences into account. The total time in the department is a practically relevant time that clinicians will find helpful in deciding which agent will reduce waiting times.

Adverse effects vary with each agent and include respiratory consequences, psychological effects, central nervous system disturbances, and nausea, gagging or vomiting. Other complications include abdominal pain, pruritis and "administration complications" (e.g., pain with injection). It is important for investigators to record all adverse events, and comment on the clinical significance of any that occur.

Physiological parameters are routinely recorded, including heart rate, blood pressure, oxygen saturation, respiratory rate and some measure of level of consciousness such as the Glasgow Coma Scale. These may be indirect reflections of the depth of sedation or of adverse events. One drawback to comparing drugs using these parameters is that physiologic measures are influenced by many other factors, including severity of pain and anxiety as well as hydration status, core temperature and other medications that may be on board.

Section 1.8: Post-sedation monitoring & discharge criteria (Table 1.6)

Once the painful or anxiety provoking procedure is completed, the patient enters a high-risk time period where there is minimal stimulation with continuing sedation/analgesia. Monitoring during this time is critical, and a patient must not be discharged until consistent, pre-defined criteria have been met (see Table 6). Patients should be observed for at least two hours if reversal agents have been administered.

Section 1.9: The Thesis approach

This thesis reports the results of a systematic review to examine the evidence for the use of pharmacological interventions for procedural sedation in children. A systematic review is an appraisal of a clearly formulated question that uses systematic and explicit methods to identify, select and critically appraise relevant research, and to collect and analyse data from the studies that are included in the review. Statistical methods (meta-analysis) may or may not be used to analyse and summarise the results of the included studies.(1) As with other study designs, systematic reviews are performed with differing methodological rigour.(2)

My goal was to conduct a systematic review according to rigorous methodological standards. At the outset, a protocol was developed in order to avoid bias in the review process. The protocol was peer-reviewed through the Cochrane Anaesthesia Review Group (CARG) and published in the Cochrane Library(22). The Cochrane Collaboration, founded in 1993 and named after Archie Cochrane, is an international, non-profit and independent organisation that produces, disseminates and updates systematic reviews of healthcare interventions. This collaboration provides up-to-date, accurate information about the effects of healthcare.

Cochrane reviews have the following general features:(3)

- A structured format helps the reader to find his/her way around the review easily;
- A detailed methods section allows the reader to assess whether the review was done in such a way as to justify its conclusions;
- The quality of clinical studies to be incorporated into a review is carefully considered, using predefined criteria;
- A thorough and systematic search strategy, which includes searches for unpublished and non-English research;
- If the data collected in a review are of sufficiently similar, they may be summarized statistically in a meta-analysis, which provides a more precise estimate of clinical effect than the results from individual studies.

The goal of this review was to explore the literature for articles pertinent to the topic "Options for procedural sedation in paediatric patients requiring painful or anxiety provoking procedures in Emergency Departments". Briefly, a comprehensive search was employed by systematically searching electronic databases (MEDLINE; Cochrane Central Register of Controlled Trials (CENTRAL/CCTR); EMBASE; etc); hand-searching relevant conference proceedings and abstracts from 1998 to 2004; checking references of relevant studies; and, contacting experts in the field. The search was not limited by language or publication status. Studies that met criteria based on design (randomized controlled trials), population (paediatric patients undergoing painful or anxiety provoking procedures) and intervention (see section above for options of pharmacological agents) were included. The search was specifically designed to identify trials reporting on the efficacy and safety associated with the individual procedural sedation agents. Following these steps, the methodological quality of the relevant studies was evaluated and reported (Chapter 2). Finally, quantitative and qualitative analyses were performed (Chapter 3).

Section 1.10: Summary

Oligo-analgesia and anxiety provoking events within the paediatric ED population are frequent problems that have short and long term negative consequences for patients, parents and health care workers. Procedural sedation is one method that employs dynamic medication titration to reduce these problems. There are currently numerous variations in the practice of procedural sedation. An understanding of the efficacy of these medications as well as their safety profiles will result in a more successful outcome for the child who will undergo a potentially painful or anxiety provoking experience in the ED.

This thesis will provide an overview of a search for relevant research in this area and detail what populations were evaluated (ages, genders, procedures performed), what agents, routes and doses were used, as well as what outcome measures were evaluated. It will summarize the quality of studies, and indicate if there was sponsorship and where it came from (e.g., Industry, government/peer-reviewed, other). The thesis will go on to summarize results of these studies, with focus on the measurement of efficacy, times and adverse outcomes. It will explain the attempt to pool the data by combining all satisfaction scores, all pain scores, all sedation scores and all measures of efficacy and adverse effects of studies that compared the same study drugs. It will wrap up by discussing future directions, including methodological design of the ideal randomized control trial to answer the question: "What is the ideal agent for performing procedural sedation in a paediatric emergency department?"

Tables

Table 1.1: ASA continuum of sedation(10):

	Minimal Sedation (Anxiolysis)	Moderate Sedation/ Analgesia ("Conscious Sedation")	Deep Sedation/ Analgesia	General Anesthesia
Responsiveness	Normal response to verbal stimulation	Purposeful* response to verbal or tactile stimulation	Purposeful* response following repeated or painful stimulation	Unarousable even with painful stimulus
Airway	Unaffected	No intervention required	Intervention may be required	Intervention often required
Spontaneous Ventilation	Unaffected	Adequate	May be inadequate	Frequently inadequate
Cardiovascular Function	Unaffected	Usually maintained	Usually maintained	May be impaired

*Reflex withdrawal from a painful stimulus is NOT considered a purposeful response.

Table 1.2: ASA physical status classification system (11)

ASA 1	A normal healthy patient
ASA 2	A patient with mild systemic disease
ASA 3	A patient with severe systemic disease
ASA 4	A patient with severe systemic disease that is a constant threat to life
ASA 5	A moribund patient who is not expected to survive without the operation
ASA 6	A declared brain-dead patient whose organs are being removed for donor purposes

Table 1.3. AAP/ASA guidelines for pre-procedural fasting for elective procedures (9)

Age, months	Solids and Non-clear Liquids, * hours	Clear Liquids, hours
<6	4–6†	2
6–36	6	2
>36	6–8‡	2

* Infant formulas, breast milk, and nonhuman milk.

† Four hours according to the AAP guidelines.

‡ Eight hours according to the AAP guidelines.

Table 1.4: Medications used for procedural sedation.
(30)

Sedative-Hypnotics:

Medication	Dose/Route	Onset of action	Duration of action
Thiopental	25mg/kg PR	5-15 minutes	60-90 minutes
Pentobarbital	1-3 mg/kg IV	1-5 minutes	15-60 minutes
	2-5 mg/kg IM	5-15 minutes	2-4 hours
	2-3 mg/kg PO	15-60 minutes	2-4 hours
Methohexital	20-30 mg/kg PR	5-15 minutes	20-90 minutes
	0.75-.0 mg/kg IV	< 1 minute	5-10 minutes
Midazolam	0.05-0.15 mg/kg IV	1-2 minutes	30-60 minutes
	0.05-0.2 mg/kg IM	2-15 minutes	30-60 minutes
	0.2-0.5 mg/kg IN	10-15 minutes	45 minutes
	0.5-1 mg/kg PR	5-15 minutes	30-60 minutes
	0.25-0.75 mg/kg PO	10-20 minutes	1-4 hours
Lorazepam	0.05-0.1 mg/kg IV	3-5 minutes	2-6 hours
	0.05-0.1 mg/kg IM	10-20 minutes	2-6 hours
	0.05-0.1 mg/kg PO	60 minutes	2-8 hours
Diazepam	0.1-0.2 mg/kg IV	2-3 minutes	30-90 minutes
	0.3-0.5 mg/kg PR	5-15 minutes	2-4 hours
Chloral hydrate	25-100 mg/kg PO/PR	15-30 minutes	2-3 hours
Propofol	0.5-1 mg/kg or 25-125 mcg/kg/minute	<1-2 minutes	3-10 minutes
Etomidate	0.1-0.3 mg/kg	<1 minute	5-15 minutes

Analgesics:

Morphine	0.05-0.1 mg/kg IV	5-10 minutes	2-4 hours
Fentanyl	1-4 mcg/kg IV	1-3 minutes	20-90 minutes
	0-5 mcg/kg TM	15-30 minutes	60-120 minutes

Combinations:

Meperidine + Promethazine + Chlorpromazine	2 mg/kg IM + 1 mg/kg IM + 1mg/kg IM	20-30 minutes	2-20 hours
Ketamine	0.5-2 mg/kg IV	1-2 minutes	15-60 minutes
	3-5 mg/kg IM	3-10 minutes	15-60 minutes
	5-10 mg/kg PO	30-45 minutes	2-4 hours
Nitrous oxide	30-50 percent	1-5 minutes	3-5 minutes

PO: oral, PR: rectal, IN: intranasal, IM: intramuscular, IV: intravenous, mg: milligram, mcg: microgram, kg: kilogram

Table 1.5: Reversal Agents.

Agent	Dose/route	Onset/ Duration	Comments
Naloxone	1-100 mcg/kg Q1-2 minutes IV, IM, ET	1-3 minutes/ 15-120 minutes	• Low dose maintains analgesia • Not effective at blocking the decreased peripheral vascular resistance
Flumazenil	0.01-0.02 mg/kg Q1-2 minutes IV	1-2 minutes/ 20-120 minutes	• May induce seizures

Q: every, IM: intramuscular, IV: intravenous, mg: milligram, mcg: microgram, kg: kilogram, ET: endotracheal

Table 1.6: Sample discharge instructions after sedation/analgesia (8)

The medicines you have received in the emergency department can sometimes cause confusion, sleepiness, or clumsiness; therefore, you need to be extra careful for the next 24 hours. If you have any questions, please do not hesitate to call the emergency department.

1. Do not leave the child unattended at any time in a car seat; if the child falls asleep in the car seat; watch the child continuously to make sure that he or she does not have any difficulty breathing.

2. No eating or drinking for at least the next 2 hours, and the child is completely awake and alert, and has no nausea. If the child is an infant, half a normal feeding may be given 1 hour after discharge.

3. If sleepy, the child should not be left alone, and should be awakened from sleep every hour for the next 4 hours. If the child's breathing does not appear normal to you or if you are unable to wake the child up, call 911, or return to the hospital, *immediately*.

4. No playing that requires coordination (bikes, skating, swing sets, climbing, monkey bars, etc) for the next 24 hours since these activities might result in the child injuring himself or herself.

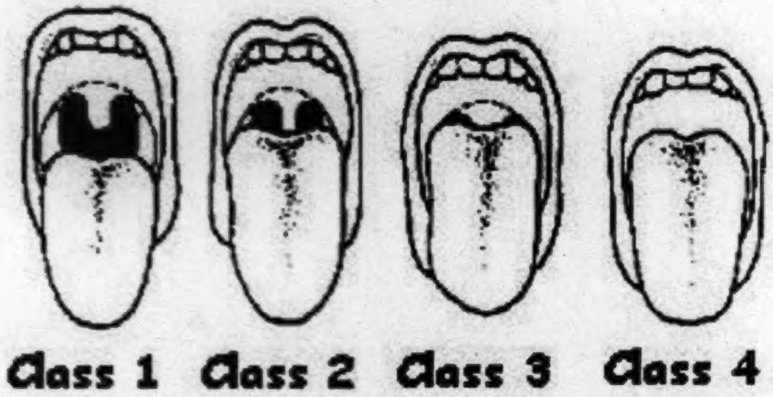
5. No swimming or using machines that might result in injury for the next 24 hours without adult supervision.

6. Supervise all playing or bathing for the next 8 hours.

7. Return immediately to the emergency department for vomiting more than once, strange or unusual behaviour, or any other symptom that does not seem normal for the child.

Figures

Figure 1.1: Mallampati classification (38)



Evaluation of the oropharynx is accomplished by asking the patient to open their mouth and stick out their tongue (but not by vocalizing).

Class I: Entire uvula and tonsillar pillars visible
Class II: Tip of uvula and pillars hidden by tongue
Class III: Only soft palate visible
Class IV: Only hard palate visible

Reference List for Chapter 1

(1) The UK National Screening Committee. Glossary for UK National Screening Programmes [on-line]. Accessed at www.nsc.nhs.uk/glossary/glossary_ind.htm on 30 January 2005.

(2) Moore A, McQuay H, Edwards J, Barden J, Derry S, McQuay M, Moor M. Bandolier Glossary of diagnostic terms. Accessed at http://www.jr2.ox.ac.uk/bandolier/booth/diagnos/glossary.html on 30 January 2005.

(3) The Cochrane Collaboration. Structure of a Cochrane Review. Accessed at http://www.cochrane.org/reviews/revstruc.htm on 12 January 2005.

(4) Agrawal D, Manzi SF, Gupta R, Krauss B. Preprocedural fasting state and adverse events in children undergoing procedural sedation and analgesia in a pediatric emergency department. Annals of Emergency Medicine 2003; 42:636-46.

(5) American Academy of Pediatric Dentistry. American Academy of Pediatric Dentistry. Guidelines for the elective use of pharmacologic conscious sedation and deep sedation in pediatric dental patients. Pediatrics 1993; 15:297-301.

(6) American Academy of Pediatrics Committee on Drugs. American Academy of Pediatrics Committee on Drugs: Guidelines for monitoring and management of pediatric patients during and after sedation for diagnostic and therapeutic procedures. Pediatrics 1992; 89:1110-5.

(7) American College of Emergency Physicians. American College of Emergency Physicians. The use of pediatric sedation and analgesia. Annals of Emergency Medicine 1993; 22:626-627.

(8) American College of Emergency Physicians. Clinical policy for procedural sedation and analgesia in the emergency department. American College of Emergency Physicians. Annals of Emergency Medicine 1998; 31:663-77.

(9) American Society of Anesthesiologists. American Society of Anesthesiologists. Practice guidelines for sedation and analgesia by non-anesthesiologists. A report by the American Society of Anesthesiologists Task Force on sedation and analgesia by non-anesthesiologists. Anesthesiology 1996; 84:459-471.

(10) American Society of Anesthesiologists. American Society of Anesthesiologists. Continuum of depth of sedation. Definition of general anesthesia and levels of sedation/analgesia. Approved by House of

Delegates on October 13, 1999. Accessed at http://www.asahq.org/publicationsAndServices/standards/20.pdf on 18 January 2005

(11) American Society of Anesthesiologists. ASA Physical Status Classification System. Accessed at http://www.asahq.org/clinical/physicalstatus.htm on 30 January 2005.

(12) Balsells F, Wyllie R, Kay M, Steffen R. Use of conscious sedation for lower and upper gastrointestinal endoscopic examinations in children, adolescents, and young adults: a twelve-year review. Gastrointestinal Endoscopy 1997; 45:375-80.

(13) Bates BA, Schutzman SA, Fleisher GR. A comparison of intranasal sufentanil and midazolam to intramuscular meperidine, promethazine, and chlorpromazine for conscious sedation in children. Annals of Emergency Medicine 1994; 24:646-51.

(14) Binder LS, Leake LA. Chloral hydrate for emergent pediatric procedural sedation: a new look at an old drug. American Journal of Emergency Medicine 1991; 9:530-4.

(15) Blackburn P, Vissers R. Pharmacology of emergency department pain management and conscious sedation. Emergency Medicine Clinics of North America 2000; 18:803-27.

(16) Brady M, Kinn S, Stuart P. Preoperative fasting for adults to prevent perioperative complications (Review). The Cochrane Library, Issue 1, 2005. Chichester, UK: John Wiley & Sons, Ltd.

(17) Brown JC, Klein EJ, Lewis CW, Johnston BD, Cummings P. Emergency department analgesia for fracture pain. Annals of Emergency Medicine 2003; 42:197-205.

(18) Cook BA, Bass JW, Nomizu S, Alexander ME. Sedation of children for technical procedures: current standard of practice. Clinical Pediatrics 31:137-42, 1992.

(19) Cote CJ, Karl HW, Notterman DA, Weinberg JA, McCloskey C. Adverse sedation events in pediatrics: analysis of medications used for sedation. Pediatrics 2000; 106:633-44.

(20) Ducharme J. Acute pain and pain control: state of the art. Annals of Emergency Medicine 2000; 35:592-603.

(21) Elliott CH, Jay SM WP. An observational scale for measuring children's distress during medical procedures. J Pediatr Psychol 1987; 12: 543-551.

(22) Evered L, Klassen TP, Hartling L, Wiebe N, Rowe BH. Options for procedural sedation in pediatric patients requiring painful or anxiety

provoking procedures in Emergency Departments (Protocol). The Cochrane Library, Issue 1, 2005. Chichester, UK: John Wiley & Sons, Ltd.

(23) Fich A, Efrat R, Sperber AD, Wengrower D, Goldin E. Nitrous oxide inhalation as sedation for flexible sigmoidoscopy. Gastrointestinal Endoscopy 1997; 45:10-12.

(24) Ghaffar S, Haverland C, Ramaciotti C, Scott WA, Lemler MS. Sedation for pediatric echocardiography: evaluation of preprocedure fasting guidelines. Journal of the American Society of Echocardiography 2002; 15:980-3.

(25) Godambe SA, Elliot V, Matheny D, Pershad J. Comparison of propofol/fentanyl versus ketamine/midazolam for brief orthopedic procedural sedation in a pediatric emergency department. Pediatrics 2003; 112(1 Pt 1):116-23.

(26) Graber RG. Propofol in the endoscopy suite: an anesthesiologist's perspective. Gastrointestinal Endoscopy 1999; 49:803-6.

(27) Green SM, Rothrock SG, Lynch EL, Ho M, Harris T, Hestdalen R et al. Intramuscular ketamine for pediatric sedation in the emergency department: safety profile in 1,022 cases. Annals of Emergency Medicine 1998; 31:688-97.

(28) Hardy JG, Lee SW, Wilson CG. Intranasal drug delivery by spray and drops. Journal of Pharmacy & Pharmacology 1985; 37:294-7.

(29) Havel CJ, Jr., Strait RT, Hennes H. A clinical trial of propofol vs midazolam for procedural sedation in a pediatric emergency department. Academic Emergency Medicine 1999; 6:989-97.

(30) Hazinski MF, ed. PALS Provider Manual. Dallas, Texas: American Heart Association, 2002.

(31) Hunt GS, Spencer MT. Etomidate and midazolam for procedural sedation: prospective trial. Annals of Emergency Medicine 2003; 42, 540.

(32) Ingebo KR, Rayhorn NJ, Hecht RM, Shelton MT, Silber GH, Shub MD. Sedation in children: adequacy of two-hour fasting. Journal of Pediatrics 1997; 131(1 Pt 1):155-8.

(33) Innes G, Murphy M, Nijssen-Jordan C, Ducharme J, Drummond A. Procedural sedation and analgesia in the emergency department. Canadian Consensus Guidelines. Journal of Emergency Medicine 1999; 17:145-56.

(34) Kennedy RM, Porter FL, Miller JP, Jaffe DM. Comparison of fentanyl/midazolam with ketamine/midazolam for pediatric orthopedic emergencies. Pediatrics 1998; 102(4 Pt 1):956-63.

(35) Kienstra AJ, Ward MA, Sasan F, Hunter JV, Morriss MC, Macias CG. Etomidate vs pentobarbital for sedation of children for head and neck CT imaging. Pediatric Emergency Care 2004; 20:499-506.

(36) Liacouras CA, Mascarenhas M, Poon C, Wenner WJ. Placebo-controlled trial assessing the use of oral midazolam as a premedication to conscious sedation for pediatric endoscopy. Gastrointestinal Endoscopy 1998; 47:455-60.

(37) Mace SE, Barata IA, Cravero JP, et al. Clinical Policy: evidence based approach to pharmacologic agents used in pediatric sedation and analgesia in the ED. Annals of Emergency Medicine 2004; 44:342-377.

(38) Mallampati SR, Gatt SP, Gugino LD, Desai SP, Waraksa B, Freiberger D et al. A clinical sign to predict difficult tracheal intubation: a prospective study. Canadian Anaesthetists' Society Journal 1985; 32:429-34.

(39) McGrath PJ, Johnson G, Goodman JT, et al. CHEOPS: a behavior scale for rating postoperative pain in children. In: Fields HL, Dubner R, Carvero Feal, editors. Advances in Pain Research and Therapy. New York, NY: Raven Press, 1985: 395-402.

(40) Napoli KL, Ingall CG, Martin GR. Safety and efficacy of chloral hydrate sedation in children undergoing echocardiography. Journal of Pediatrics 1996; 129:287-91.

(41) Ng KC, Ang SY. Sedation with ketamine for paediatric procedures in the emergency department--a review of 500 cases. Singapore Medical Journal 2002; 43:300-4.

(42) Okutan V, Lenk MK, Sarici SU, Dundaroz R, Akin R, Gokcay E. Efficacy and safety of rectal thiopental sedation in outpatient echocardiographic examination of children. Acta Paediatrica 2000; 89:1340-3.

(43) Overbaugh R, Jones P, Nguyen A, Swaney G. Effect of mixed versus unmixed lidocaine with propofol. The Internet Journal of Anesthesiology 2003; 7(2).

(44) Proudfoot J. Analgesia, anesthesia, and conscious sedation. Emergency Medicine Clinics of North America 1995; 13(2):357-79.

(45) Ramsay MA, Savege TM, Simpson BR, Goodwin R. Controlled sedation with alphaxalone-alphadolone. British Medical Journal 1974; 2:656-9.

(46) Roth KR, Herr SM, Pitetti RD, Zucherbraun NS, Fine GF, King C. Comparison of etomidate and fentanyl with midazolam and fentanyl for sedation and analgesia during fracture in a pediatric ED (Abstract). Pediatric Academic Society/Society of Pediatric Research Annual Meeting; May, 2004.

(47) Sacchetti A, Schafermeyer R, Geradi M, Graneto J, Fuerst RS, Cantor R et al. Pediatric analgesia and sedation. Annals of Emergency Medicine 1994; 23:237-50.

(48) Schechter N, Berde C, Yaster M, eds. Pain in Infants, Children, and Adolescents. Baltimore, Md: Williams & Wilkins, 1993.

(49) Schutzman SA, Liebelt E, Wisk M, Burg J. Comparison of oral transmucosal fentanyl citrate and intramuscular meperidine, promethazine, and chlorpromazine for conscious sedation of children undergoing laceration repair. Annals of Emergency Medicine 1996; 28:385-90.

(50) Sherwin TS, Green SM, Khan A, Chapman DS, Dannenberg B. Does adjunctive midazolam reduce recovery agitation after ketamine sedation for pediatric procedures? A randomized, double-blind, placebo-controlled trial. Annals of Emergency Medicine 2000; 35:229-38.

(51) Smith C, Rowe RD, Vlad P. Sedation of children for cardiac catheterization with an ataractic mixture. Canadian Anaesthetists' Society Journal 1958; 5:35-40.

(52) Sobel RM, Morgan BW, Murphy M. Ketamine in the ED: medical politics versus patient care. American Journal of Emergency Medicine 1999; 17:722-

(53) St.Germaine Brent A. Acute pain in children: the management of pain in the emergency department. Pediatric Clinics of North America 2000; 47: 487-755.

(54) Terndrup TE. Pediatric pain control. Annals of Emergency Medicine 1996; 27:466-70.

(55) Terndrup TE, Dire DJ, Madden CM, Davis H, Cantor RM, Gavula DP. A prospective analysis of intramuscular meperidine, promethazine, and chlorpromazine in pediatric emergency department patients. Annals of Emergency Medicine 1991; 1:31-35.

(56) Vertesi L. Coincidence, conscious sedation, CAEP and ketamine. Canadian Journal of Emergency Medicine Internet Letters to the Editor 2000; 2(1). Accessed at http://www.caep.ca/004.cjem-jcmu/004-00.cjem/vol-2.2000/v21-009.htm on 30 January 2005

(57) Walco GA, Cassidy RC, Schechter NL. Pain, hurt, and harm. The ethics of pain control in infants and children. New England Journal of Medicine 1994; 331:541-4.

(58) Wathen JE, Roback MG, Mackenzie T, Bothner JP. Does midazolam alter the clinical effects of intravenous ketamine sedation in children? A double-

blind, randomized, controlled, emergency department trial. Annals of Emergency Medicine 2000; 36:579-88.

(59) Weisman SJ, Bernstein B, Schechter NL. Consequences of inadequate analgesia during painful procedures in children. Archives of Pediatrics & Adolescent Medicine 1998; 152:147-9.

(60) Wilbur K. Is propofol an optimal agent for procedural sedation and rapid sequence intubation in the emergency department? Canadian Journal of Emergency Medicine 2001; 3:302-310.

(61) Wilson JA, Kendall JM, Cornelius P. Intranasal diamorphine for paediatric analgesia: assessment of safety and efficacy. Journal of Accident & Emergency Medicine 1997; 14:70-2.

(62) Wright SW, Chudnofsky CR, Dronen SC, Kothari R, Birrer P, Blanton DM et al. Comparison of midazolam and diazepam for conscious sedation in the emergency department. Annals of Emergency Medicine 1993; 22:201-5.

Chapter Two: Methods of review and quality of included studies

Section 2.1: Introduction

A hierarchy of research designs has been proposed to guide assessment of therapeutic interventions.(16) The highest level of quality is the "N of 1 randomized controlled trial", otherwise known as "single sample research designs" (SSRD). SSRD involves studying a single individual by taking repeated measurements of one or more dependent variables and systematically applying the independent variable in a random fashion. This study design is most appropriate for chronic illnesses, but is inappropriate for studying self-limited conditions or certain procedures (e.g., definitive treatments such as surgery). The next designs in the hierarchy of strength of evidence are systematic reviews of randomized trials and single, large, randomized trials. Given the nature of much of the clinical trial data in many areas of medicine where multi-centered definitive trials are not performed, systematic review evidence is indeed feasible as a strategy to evaluate the efficacy of different treatment regimens. Systematic reviews conducted according to explicit and rigorous methods provide empirical answers to focused questions about the efficacy of different treatment regimens and also help to identify gaps in the available evidence.

The objective of this specific review is to evaluate the efficacy of medications that are commonly used for procedural sedation in paediatric patients requiring painful or anxiety-provoking procedures in emergency departments.

The objective of this chapter is to describe the methods used for the systematic review and to describe the results of the search and the methodological quality of the studies that were identified for inclusion in the review. The results of the systematic review are presented in Chapter 3.

Section 2.2: Methods of the review

Prior to beginning this systematic review, a structured protocol was developed.(12) This protocol specified the criteria for including studies in the review (i.e., the types of studies, participants, interventions, and outcome measures). A search strategy for identification of studies was described and the methodology was detailed, including our approach to assessing methodological quality, data extraction, and analysis.

2.2.1 Criteria for including studies in the review

2.2.1.1 Study Populations

Studies including paediatric patients, aged one month to 18 years, undergoing sedation with or without analgesia for a procedure that was anticipated to be painful or anxiety provoking were considered for inclusion in this overview. Studies recruiting paediatric and adult participants were considered, with the intention of only including data for the paediatric cases.

Studies including only patients recruited in emergency departments (or their equivalent) were considered.

2.2.1.2 Interventions

In order to be included in this review, the study had to randomize patients to receive a sedative, placebo or comparative agent for the purpose of procedural sedation.

2.2.1.3 Outcome measures

While all patient outcomes were considered, the primary outcome was efficacy as judged by a sedation score. Other measures of efficacy also were examined, including behavioural measures (e.g. pain score), success of procedure (which may indirectly reflect success of sedation), and patient/parent/healthcare provider satisfaction. Times including onset of action, duration of effect and recovery period were also evaluated. Adverse effects during or following sedation (e.g. pain on injection) and physiological parameters (e.g. oxygen saturation) were also assessed. Studies were not included if they did not evaluate at least one of these outcome measures.

2.2.1.4 Types of studies

To be considered for inclusion, clinical studies had to be randomized controlled trials (RCTs). This included both completed and ongoing trials.

2.2.2 Search strategy

Studies were identified by systematically searching the following electronic databases: MEDLINE (1966 to April, 2004), CENTRAL/CCTR (2nd quarter, 2004), EMBASE (1988 to April, 2004), and Dissertation Abstracts (April, 2004). The search strategies used are detailed in Appendix 2.1.

Additional trials were sought by hand-searching relevant conference proceedings and abstracts from 1998-2004 inclusive (Society of Pediatric Research/Pediatric Academic Society, American College of Emergency Physicians, Society of Academic Emergency Medicine and Canadian Association of Emergency

Physician); contacting known trialists, experts and seven medical/pharmaceutical companies (Novopharm, Astra-Zeneca Canada Inc., Sabex, Pfixer Canada Inc., Abbott, Janssen-Cilag, Bedford Labs); and screening the reference lists of included studies.

The search was not limited by language or publication status.

2.2.3 Study Identification

Two researchers (Lisa Hartling {LH}; Lisa Evered {LE}) each examined the output generated from the computerized search. The full manuscripts for all potentially relevant articles were obtained. The full text of each study was assessed independently by the same two reviewers using a structured form (Appendix 2.2) that outlined criteria for inclusion in terms of: population, intervention, outcome, and study design. Disagreements were resolved by consensus.

2.2.4 Quality Assessment of Included Studies (Appendix 2.3)

Methodological quality assessment was performed using three methods that were recommended by the Anaesthesia Review Group of the Cochrane Collaboration. First, each study was assessed using the validated 5-point scale described by Jadad(22)(see Appendix 2.3). In this scale, one point is allocated if the study is described as randomized, one if it states that it is double-blinded and one if the authors describe withdrawals and dropouts. Extra points (one each) are awarded if the randomization and blinding are both described and appropriate, and one point each is deducted if the study described inappropriate methods of randomization and/or blinding.

Second, for each trial, allocation concealment(40)(see Appendix 2.3) was assessed and scored as adequate, unclear or inadequate. Allocation of treatment assignment is adequately concealed if no person can identify which group the subject will be assigned to before the assignment has been performed. The allocation process should be resistant to any influence by the individual administering the treatment by having the randomization process administered by someone who is not responsible for recruiting subjects. Examples of adequate allocation concealment include: when the randomization is performed centrally; the drugs are prepared by pharmacy; the containers are serially numbered or coded; and/or numbered, opaque, sealed envelopes are used to conceal patient assignments. If the subjects are alternately assigned to a study group, or case record numbers, birth dates or day of the week are used, researchers will have a good chance of knowing which group the subject has been allocated to. This is deemed "inadequate" allocation concealment. Studies were rated "unclear" if the approach to allocation concealment was not described or if the description did not fit either "adequate" or "inadequate".

The final method used to assess methodological quality was a non-validated tool used by the Cochrane Anaesthesia Review Group (CARG)(see Appendix 2.3). The Quality of Concealment of Allocation (QoCoA) tool includes 8 items that are potentially related to bias and provides an overall score ranging from 0 to 10, with 10 being highest quality.

Two reviewers performed quality assessment independently and kappa scores were calculated to measure the agreement in scores between reviewers.(7)

2.2.5 Data Extraction

A standard form (Appendix 2.4) was used to collect the following information: characteristics of the study (e.g. design, method of randomization, withdrawals/dropouts); participants (age, gender); intervention (type, dose, route of administration, total dose administered, co-interventions); control (agents and dose); outcomes (type of efficacy measures, timing of outcomes, adverse effects); and results. Attempts were made to contact study primary investigators to obtain additional data when required.

2.2.6 Data Analysis

The methods of data analysis will be described in the Chapter 3.

Section 2.3: Results of search

2.3.1 Numbers of studies found (Figure 2.6)

The initial search resulted in 965 studies from MEDLINE/EMBASE/CENTRAL, 15 from conference proceedings, 383 from Dissertation Abstracts, zero from pharmaceutical companies and zero from experts in the field, for a total of 1363 studies. No unpublished trials were discovered, other than those reported within the conference proceedings. Of the 1363 articles reviewed, 35 trials met the inclusion criteria for this review. These included four studies that were published in abstract form only (to date).

2.3.2 Characteristics of excluded studies

One study that met the inclusion criteria but was later excluded on closer evaluation was done by McGlone(32), which was pseudo-randomized, as the investigators alternated patients allocated to each group as they were entered into the study. The other study that was excluded only after contacting the investigator did not include any paediatric patients.(6)

2.3.3 Characteristics of included studies

Thirty-five randomized controlled trials fulfilled the inclusion criteria; these were published from 1989(14) to 2004.(31)

2.3.3.1 Populations evaluated

Participants ranged in age from 4.5 months to 18 years old. The abstract presented by Hunt and Spencer(27) included patients over 10 years old, however the mean ages were 42 and 55 years in the two study groups. The authors were contacted but further details were not provided.

Procedures included laceration repair, fracture reduction, foreign body removal, burn dressings, paraphimosis reduction, emergency dental procedures, incisions and drainage, emergency computed tomography, lumbar punctures, and avulsion repairs.

2.3.3.2 Interventions that were compared (Table 2.1)

There was great variety in the agents used as well as their routes of administration. Nine studies evaluated opiates (three transmucosally (TM), five intravenously (IV), one intranasally (IN)); two groups of authors examined intravenous propofol(15;18) and 11 studies compared ketamine with other agents (two orally (PO), seven IV, one intramuscularly (IM), and one IV versus IM ketamine). Six studies examined the classic IM cocktail meperidine, promethazine and chlorpromazine (MPC).(4;17;35;36;42;46)

Twenty-five studies evaluated benzodiazepines: alone (15 studies) or in combination with another agent (eight studies), or alone versus in combination with another agent.(28;30) The most common benzodiazepine to be studied was midazolam (24/25 studies). Benzodiazepines were contrasted with every other agent commonly used (see Table 2.2). The most common method of delivery of benzodiazepines was IV (12 studies), and nine studies evaluated PO benzodiazepines, five delivered them IN and they were given per rectum (PR) in two studies.

Four studies that evaluated inhaled nitrous oxide(5;14;31;32) and three studies compared barbiturates to another medication (PR versus MPC(35), IV versus midazolam(34) and IV versus etomidate(27)). Three abstracts have been presented on use of IV etomidate, two compared with benzodiazepines(20;27;39) and one with a barbiturate.(27)

Eight studies judged different sedatives against placebo.

2.3.3.3 Outcome measures used

Similar variation was observed in the outcomes that were evaluated in the included trials. Sedation score was the primary outcome sought for this systematic review. There were 10 studies that utilized some form of sedation score including:

1. Sedation score of 1 to 5 points as scored by the nurse(1);
2. 10 centimetre visual analog sedation score reported by the physician(1);
3. 10.2 centimetre linear visual analog score on sedation by both nurses and physician(46);
4. 5-point sedation scale(17;37;49);
5. Scale of 1 to 5(24) that was reported as "best sedation score" achieved;
6. Ramsay sedation score (from 1 to 6)(18;34);
7. Scale of 1 to 10 judging the quality of sedation(20);
8. 4-point sedation score(35).

Efficacy was also determined using many other behavioural measurements, including various pain scores (Children's Hospital of Eastern Ontario Pain Score (CHEOPS), Visual Analog Scale (VAS), 10-point pain scale); distress scores (OSBD-R, a four point and a 10 distress scale, the Procedure Behavioral CheckList score, VASs and the cry, motion and struggle scores used by Theroux in 1993(47)); anxiety scores (scales of one to four or one to five, and VASs); and satisfaction scores (healthcare worker, MD, RN and/or orthopaedist). Less commonly used were outcome measurements such as activity scores(26;41;42), tolerance(5) or cooperation scores(8), and success or ease of procedure.(1;27;41)

Physiological parameters were routinely recorded, including heart rate, blood pressure, oxygen saturation, respiratory rate and some measure of level of consciousness such as the Glasgow Coma Scale (although it was not designed for use in this setting). Many studies recorded onset of sedation or time needed to start the procedure, duration that it took to complete the procedure, length of sedation, time from administration of study drug until recovery or disposition. Adverse effects were usually noted, varying from vomiting to dysphoric reactions. These events were rare and no study was powered to compare different study drugs on this outcome measure.

Section 2.4: Methodological quality of the included trials

2.4.1 Jadad score (Table 2.4)

The agreement between the reviewers on the Jadad scores was almost perfect, with a weighted kappa of 0.98. The median Jadad score was 3, (interquartile range: 1-4; range: 1-5). The numbers of studies for each score were as follows (where 5 indicates highest quality): 0 (n=0), 1 (n=9), 2 (n=4), 3 (n=11), 4 (n=4), 5 (n=7). The details of the scores are outlined in Table 2.3.

The methods of randomization were described and appropriate in 19 (54%) studies. Six studies randomized patients using computer generated technique(1;5;24;34;43;44), six by a random numbers table(4;19;27;35;37;48), one used the Moses-Oakford algorithm of randomization in blocks of ten(18), two used a random number generator(25;30), and five stated randomization was done by a schedule in pharmacy (a table was used in the trial by Hennes(19) as cited above).(28;41;42;46) The remaining 16 did not specify how randomization was performed.

In five articles (four that were described as blinded(20;25;39;47); one where it was not stated(31)), it was difficult to determine who was blinded. Three trials were not blinded(26;34;41), four studies(17;30;38;42) were single blinded. Six trials(1;4;13;15;27;45) were double blinded and the remaining seventeen trials were triple blinded. Of the 20 studies that stated that blinding was used, 15 described an appropriate method of blinding.

Twenty trials reported on withdrawals/dropouts.

2.4.2 Allocation concealment (Figure 2.1)

Agreement between reviewers on allocation concealment was good, with a kappa of 0.74. Allocation concealment was inadequate for one study.(15) Allocation concealment was adequate for 21 studies; and unclear for the remaining 13.

2.4.3 QoCoA (Figure 2.2)

Agreement between the two reviewers on the QoCoA tool was moderate, with weighted kappa of 0.56. Overall, the studies achieved better scores with this larger scale. The average (median) score was 8, (interquartile range: 6.75-9; range: 3-10).

2.4.4 Agreement of the different quality rating systems

The different rating systems did not always award the same articles the higher scores. Frequently, studies scored well on one quality measure but poorly on another.

There was only one study(15) that had inadequate concealment, and scored well (arbitrarily defined as at least seven out of 10) on QoCoA. In contrast, 21 articles had adequate concealment, and all but one scored at least 7/10 on the QoCoA scores. The other study scored 5/10.(41) The remaining 13 papers were unclear about the concealment of allocation, and the QoCoA scores of these spanned the spectrum from a score of three (two studies) to a score of nine (one study). Only five of these 13 studies scored at least 7/10 with the QoCoA score.

The Jadad score of the study that inadequately concealed allocation was 1/5.(15) The Jadad scores of 17 (81%) of the 21 studies with adequately concealed allocation were good (3-5/5). 9/13 (69%) papers that were rated as being unclear about concealment of allocation achieved only less than or equal to 2/5 on the Jadad score, and the range of Jadad scores extended from 1/5 to 5/5.

Of the 26 studies that scored well on the QoCoA, five scored poorly (0-2) on the Jadad system (Figure 2.3). On the other hand, when the articles that scored poorly on the QoCoA (less than or equal to a score of six) were looked at, eight of the nine also got a Jadad score of less than or equal to two (Figure 2.4).

2.4.5 Sponsorship

Sponsorship refers to a situation where a study has been sponsored financially by a group or company that may benefit from one particular outcome. It has been demonstrated that when a group with a vested interest funds research, the conclusions are biased to be more favourable for the product manufactured by that group.(3) This review found that 28 of the RCTs did not report any funding at all; one reported support by government grant(25), three were funded by the hospital or local research committee(1;15;19) and three were industry sponsored.(14;28;42)

Two(28;42) of the three industry sponsored studies found results that were unfavourable to the sponsor. In the RCT that compared N_2O to placebo(14), the N_2O machine was provided by the company that manufactures N_2O machines. These authors concluded that N_2O is superior to placebo. While this may be the case, the study is at risk of sponsorship bias. Klein (28) studied the addition of fentanyl lozenges to oral midazolam. They found unfavourable results for the fentanyl group despite the drugs being provided by the manufacturer of Fentanyl Oralet. The study by Schutzman(42) was sponsored by a company that develops and commercializes products for oral transmucosal delivery. The conclusions of this study were not favourable for the oral transmucosal drug.

Section 2.5: Discussion

A large number of research studies have been published on the topic of procedural sedation for paediatric patients in the ED, including 35 RCTs relevant to this systematic review. There were no published systematic reviews to date in this area. The best evidence available is included in the RCTs, which are of variable quality due to pitfalls common to many trials, such as confounding by factors that could have been avoided by appropriate randomization and blinding.

2.5.1 Deficiencies in allocation concealment

Reporting of concealment of allocation in this group of studies was variable. Only one study(15) was identified where concealment was clearly *not* performed; however, in 13 (37%) studies it was unclear if concealment was attempted. Overall, 21 (60%) clearly described the concealment of allocation adequately. This is an area of methodology that must be addressed in future research since without such concealment, there is a greater risk of selection bias, as the subject and/or physician may learn which study group the subject will be entered in before the moment of assignment. This leaves open the possibility that the researchers (unconsciously or otherwise) could influence which patients were assigned to a given intervention group. Moreover, it has been shown that studies with inadequate allocation concealment may overestimate treatment effects by as much as 40%.(40)

2.5.2 Deficiencies in randomization

Since randomization is the only method to balance all known and unknown confounders in a clinical trial, the quality of a study is directly related to the adequacy of the randomization process. There are many methods described to complete randomization, including computerized random numbers or a random numbers table. This was adequately described and appropriate in only one half of the RCTs in this systematic review. The remaining 49% of the studies did not describe their technique in sufficient detail, despite claiming to be randomized. It has been demonstrated that failure to randomize may increase or decrease estimates of effect. The distorted estimate may be as large or larger than true effects, making it challenging to draw conclusions based on studies that are not randomized.(29) This can explain why discrepancies in magnitude of treatment effect occur between studies(21), and why research occasionally reaches conflicting conclusions.(9)

2.5.3 Deficiencies in blinding

The purpose of blinding is to eliminate sources of bias, achieved by keeping subjects and/or observers unaware of the group to which the subjects are assigned. By blinding, investigators protect against the possibility that knowledge of which group the patient is in may affect a subject's response to a treatment, the doctors', nurses', and caregivers' behaviours (known as "performance bias") or the assessment of the outcome variables (known as "detection bias"). There are six groups in any trial that can be blinded: patients, health care providers, data collectors, data analysts, outcome assessors and personnel writing the paper.(10) The Cochrane Collaboration uses the following definitions for different levels of blinding(2). In single-blind trials, the participant is unaware of the study group he or she has been assigned to, aiming to prevent performance bias. A study is double-blinded if both subject and outcome assessor are blinded, which has the added protection against detection bias. The Cochrane Collaboration describes triple blinding as "an expression that is sometimes used to indicate that knowledge of which study participants are in which comparison group is kept secret from the statistician doing the analysis". It is difficult to interpret studies with no blinding whatsoever, as well as those that had not blinded the subject, as the subject, parent, nurse or physician may have a preconceived notion of which drug they preferred.

Consistent with other literature(10), there was marked variability of the levels of blinding across the 35 RCTs in this review. The most frequent number of groups blinded in the studies was three, indicating that researchers in this area tend to value blinding. The studies that had inadequate blinding must be interpreted carefully, as bias may have occurred. One group of researchers compared double-blind trials with other trials(11) and found discordant results. Specifically, there was an average of 12% more beneficial effect in trials of lower methodological quality (95%CI: 25% more beneficial to 4% less). When evaluating meta-analyses, pooled effect estimates were 100% more to 493% less beneficial if the trial was not double-blinded.

2.5.4 Overall interpretation

Quality assessment is challenging for a variety of reasons. The different scoring systems did not always reach the same conclusions; however, there were a few patterns where studies achieved good allocation concealment scores as well as QoCoA, and Jadad scores. The lack of perfect correlation between the scoring systems does not imply that the scales were not valid, but could imply that they measure different things. The Jadad score has been "validated"; the QoCoA has not been.

These discrepancies are consistent with recent research done in this area(2), specifically comparing quality scores using different tools and highlighting the inconsistencies. Problems with using quality scales include the following: there is no gold standard available to validate a specific scale; there is often confusion between the level of reporting and the actual design and conduct of a trial; scales often include items that are not empirically proven to be related to quality. An example of this occurs with the QoCoA, which reports, "inclusion and exclusion criteria were/not clearly defined in the text", an item that relates more to applicability than quality. Finally, many scales report a summary score, that permits simple comparisons but are not evidence based.(23) The bottom line is that while these scales do provide some guide to assess quality, validity and applicability, they must be used with caution and relevant aspects of each scale should be interpreted individually.

Section 2.6: Summary

This chapter demonstrates that while literature on procedural sedation in emergency paediatrics is common, the quality of the trials is variable and often poor. Although there were 35 trials reporting to be randomized, only half described adequate techniques of randomization, and only 45% adequately described the level of blinding. The implication is that it is possible that the results and conclusions reached by the researchers involved in some studies may be less valid. It is therefore important to consider methodological quality when interpreting the results of the component studies.

The other important finding from this evaluation is that results of quality assessment varied based on the different quality assessment tools used. In this evaluation, we employed three separate measures of quality that are felt to be valid and/or reliable. In many cases a trial was considered high quality by all three scoring systems. Two points can be learned from this: 1) that the different quality assessment tools provide different information, and this information does not necessarily correlate between the scoring systems; and 2) that when designing a trial, investigators should ensure quality on multiple levels. Applying these three quality scores to a study design before commencing the research may be a helpful start in achieving the ideal design.

It may be more important to evaluate components that are known to be related to bias rather than using composite scales or scores that include items for which there is no empirical evidence to show that they are associated with biased treatment estimates. Systematic reviews (in particular the Cochrane Collaboration) are moving away from using summary tools (checklists, scales, scores) towards component-based approach to quality assessment. Perhaps reviewers should be cautioned about using tools that have not been validated (e.g., QoCoA).

Tables

Table 2.1: Number of studies comparing different types of sedatives

	Opiates	**Benzodiazepines**	**Ketamine**	**Other**
Opiates	1	5	2	3
Benzodiazepines	5	4	6	14
Ketamine	2	6	1	3
Other	3	14	3	6

Table 2.2: Different agents compared with benzodiazepines

Benzodiazepine compared to	**Number of studies**
Ketamine	6
Opiates	5
Etomidate	2
Propofol	2
Nitrous oxide	2
MPC	2
Pentobarbital	1
Placebo	5
Different doses of benzodiazepines	2
Different routes of benzodiazepines	1
Different benzodiazepines by different routes	1

Table 2.3: Quality scores

Authors Year	R (max 2)	B (max 2)	W (max 1)	Jadad (max 5)	C	QoCoA (max 10)
Acworth 2001	2	0	1	3	A	10
Bates 1994	2	0	1	3	U	9
Burton 1998	2	2	1	5	U	7
Connors 1994	1	1	1	3	A	8
Davies 1998	1	1	0	2	A	9
Everitt 2002	1	0	0	1	U	7
Fatovich 1995	1	2	0	3	A	10
Gamis 1989	1	2	1	4	U	6
Godambe 2003	0	0	1	1	I	7
Hart 1997	1	0	0	1	U	6
Havel 1997	2	0	1	3	U	7
Hennes 1990	2	2	1	5	A	10
Hunt 2003	1	1	0	2	U	4
Kanegaye 2003	2	2	1	5	A	10
Kennedy 1998	2	0	0	2	A	10
Kharasch 2000	1	0	0	1	U	3
Kienstra 2003	2	2	1	5	A	8
Klein 2002	1	2	0	3	A	10
Luhmann 2001	2	0	1	3	A	9
Luhmann 2004	1	0	0	1	U	5

Authors Year	R (max 2)	B (max 2)	W (max 1)	Jadad (max 5)	C	QoCoA (max 10)
Moro-Sutherland 2000	2	0	1	3	A	7
O'Brien 1991	2	2	0	4	A	10
Petrack 1996	1	2	0	3	U	8
Qureshi 1995	2	2	0	4	U	9
Roback 2002	1	0	0	1	U	4
Roth 2004	1	0	0	1	U	3
Schutzman 1994	1	0	1	2	U	5
Schutzman 1996	1	0	0	1	A	8
Shane 1994	2	2	1	5	A	10
Sherwin 2000	2	2	1	5	A	9
Taiwo 1992	1	1	0	2	U	5
Terndrup 1993	2	2	0	4	A	9
Theroux 1993	1	2	0	3	A	9
Wathen 2000	2	2	1	5	A	8
Younge 2000	1	1	1	3	A	10

Randomization (R), Blinding (B) = 0, 1 or 2 (Jadad scale)
Withdrawal (W) = 1 or 0 (Jadad scale)
Concealment (C) = adequate (A), unclear (U) or inadequate (I)
Quality of Concealment of Allocation (QoCoA) = 0-10

Table 2.4: Jadad Scores of Included 35 Randomized Controlled Trials

Jadad Score	Number of RCTs (% out of t=35)	
1	9 (26)	
2	4 (11)	
3	11 (32)	22 (63%)
4	4 (11)	
5	7 (20)	

Figures

Figure 2.1: Allocation Concealment Scores

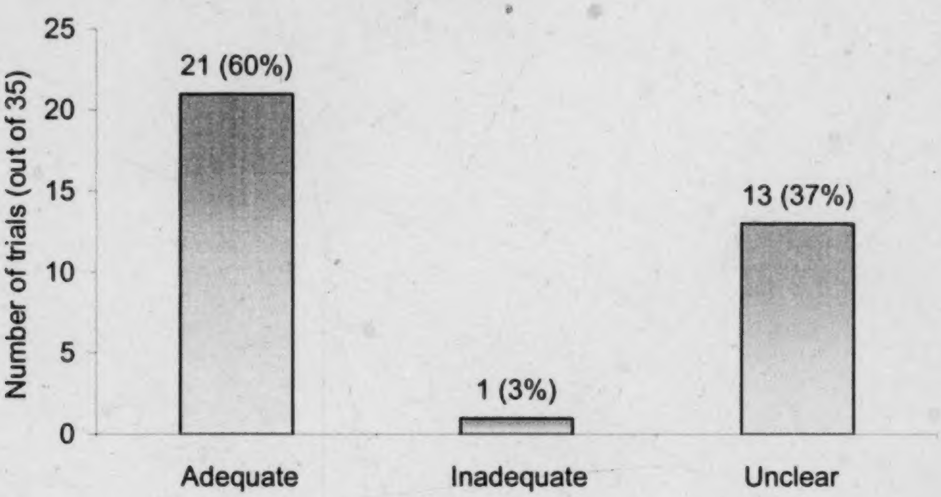


Figure 2.2: Quality of Concealment of Allocation Scores

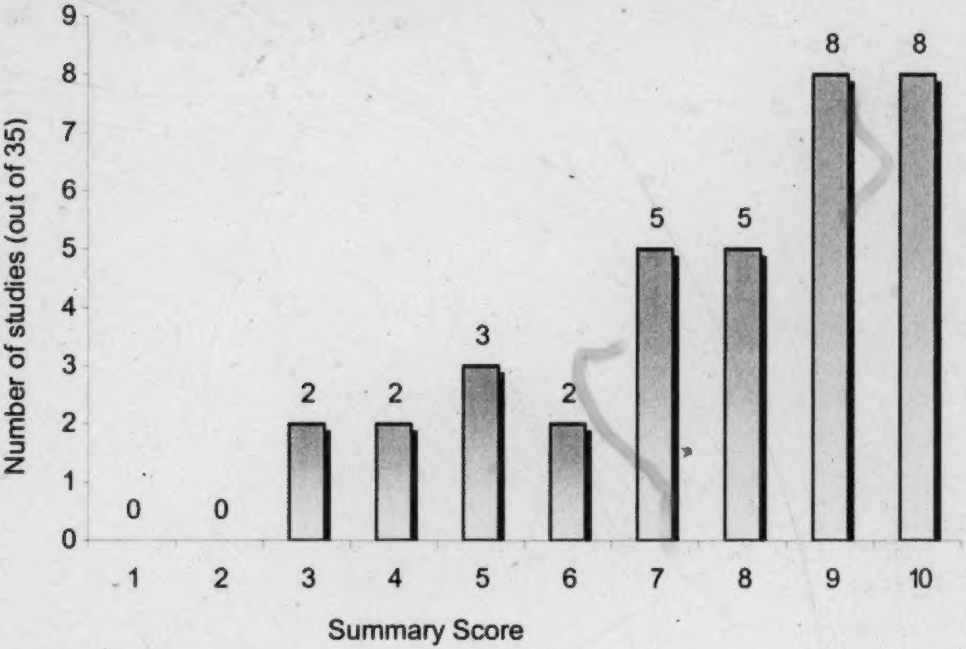
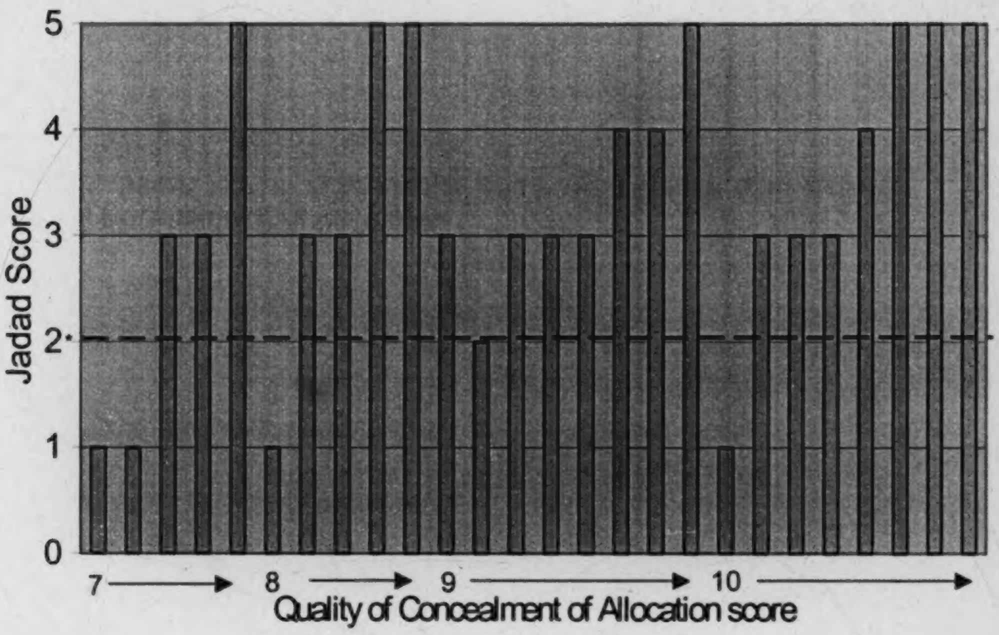
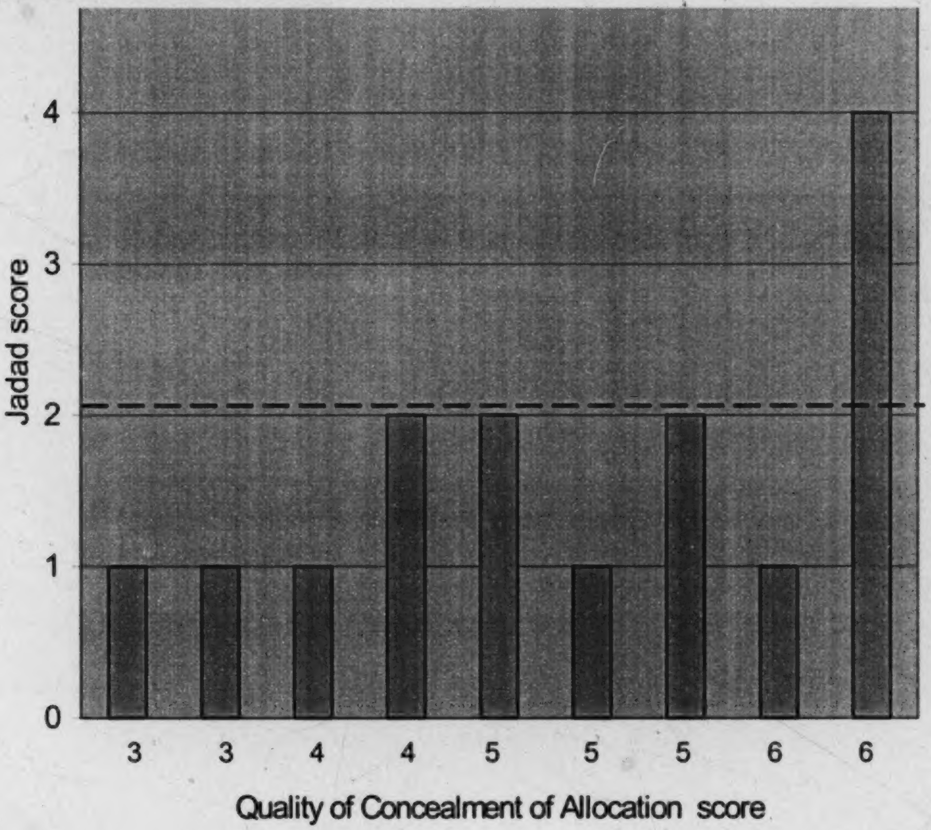


Figure 2.3: Jadad scores of 26 studies that scored greater than 6/10 on Quality of Concealment of Allocation



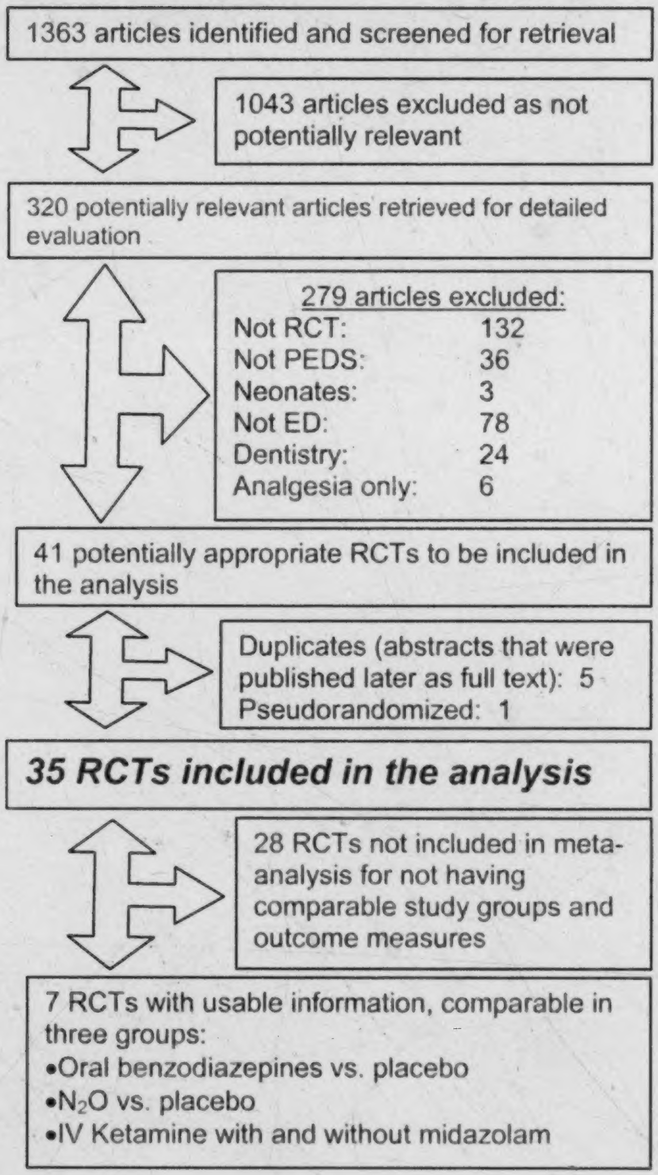
*Jadad Score of 0-2 is considered poor

Figure 2.4: Jadad scores of 9 studies that scored less than 7/10 on Quality of Concealment of Allocation



*Jadad Score of 0-2 is considered poor

Figure 2.5: QUORUM flow chart of retrieved articles (33)


1363 articles identified and screened for retrieval
1043 articles excluded as not potentially relevant
320 potentially relevant articles retrieved for detailed evaluation
279 articles excluded:
Not RCT: 132
Not PEDS: 36
Neonates: 3
Not ED: 78
Dentistry: 24
Analgesia only: 6
41 potentially appropriate RCTs to be included in the analysis
Duplicates (abstracts that were published later as full text): 5
Pseudorandomized: 1
35 RCTs included in the analysis
28 RCTs not included in meta-analysis for not having comparable study groups and outcome measures
7 RCTs with usable information, comparable in three groups:
•Oral benzodiazepines vs. placebo
•N2O vs. placebo
•IV Ketamine with and without midazolam

Reference List for Chapter 2

(1) Acworth JP, Purdie D, Clark RC. Intravenous ketamine plus midazolam is superior to intranasal midazolam for emergency paediatric procedural sedation. Emergency Medicine Journal 2001; 18:39-45.

(2) Alderson P, Green S, Higgins JPT, eds. Formulating the problem. Cochrane Reviewers' Handbook 4.2.2 [updated December 2003]; Glossary. http://www.cochrane.org/resources/handbook/hbook.htm (accessed 31st January 2005).

(3) Baker CB, Johnsrud MT, Crismon ML, Rosenheck RA, Woods SW. Quantitative analysis of sponsorship bias in economic studies of antidepressants. British Journal of Psychiatry 2003; 183:498-506.

(4) Bates BA, Schutzman SA, Fleisher GR. A comparison of intranasal sufentanil and midazolam to intramuscular meperidine, promethazine, and chlorpromazine for conscious sedation in children. Annals of Emergency Medicine 1994; 24:646-51.

(5) Burton JH, Auble TE, Fuchs SM. Effectiveness of 50% nitrous oxide/50% oxygen during laceration repair in children. Academic Emergency Medicine 1998; 5:112-7.

(6) Perry S, Godwin S, Bobbett C. A direct comparison of etomidate and midazolam during procedural sedation (Abstract). Academic Emergency Medicine 2004; 5:494.

(7) Cohen JA. A coefficient of agreement for nominal scales. Educ Psych Meas 1960; 20:37-46.

(8) Connors K, Terndrup TE. Nasal versus oral midazolam for sedation of anxious children undergoing laceration repair. Annals of Emergency Medicine 1994; 24:1074-9.

(9) Deeks JJ, Dinnes J, D'Amico R, Sowden AJ, Sakarovitch C, Song F et al. Evaluating non-randomised intervention studies. Health Technology Assessment 2003; 7:iii-x, 1-173.

(10) Devereaux PJ, Manns BJ, Ghali WA, Quan H, Lacchetti C, Montori VM et al. Physician interpretations and textbook definitions of blinding terminology in randomized controlled trials. JAMA 2001; 285:2000-3.

(11) Egger M, Juni P, Bartlett C, Holenstein F, Sterne J. How important are comprehensive literature searches and the assessment of trial quality in systematic reviews? Empirical study. Health Technology Assessment 2003; 7:1-76.

(12) Evered L, Klassen TP, Hartling L, Wiebe N, Rowe BH. Options for procedural sedation in pediatric patients requiring painful or anxiety provoking procedures in Emergency Departments (Protocol). The Cochrane Library, Issue 1, 2005. Chichester, UK: John Wiley & Sons, Ltd.

(13) Everitt IJ, Barnett P. Comparison of two benzodiazepines used for sedation of children undergoing suturing of a laceration in an emergency department. Pediatric Emergency Care 2002; 18:72-4.

(14) Gamis AS, Knapp JF, Glenski JA. Nitrous oxide analgesia in a pediatric emergency department. Annals of Emergency Medicine 1989; 18:177-81.

(15) Godambe SA, Elliot V, Matheny D, Pershad J. Comparison of propofol/fentanyl versus ketamine/midazolam for brief orthopedic procedural sedation in a pediatric emergency department. Pediatrics 2003; 112:116-23.

(16) Guyatt G, Haynes B, Jaeschke R, Cook D, Greenhalgh T, Meade M et al. Introduction: the philosophy of evidence-based medicine. In: Guyatt G, Rennie D, editors. Users' guides to the medical literature - a manual for evidence-based clinical practice. Chicago, Ill: AMA Press, 2002: 3-12.

(17) Hart LS, Berns SD, Houck CS, Boenning DA. The value of end-tidal CO_2 monitoring when comparing three methods of conscious sedation for children undergoing painful procedures in the emergency department. Pediatric Emergency Care 1997; 13:189-93.

(18) Havel CJ, Jr., Strait RT, Hennes H. A clinical trial of propofol vs midazolam for procedural sedation in a pediatric emergency department. Academic Emergency Medicine 1999; 6:989-97.

(19) Hennes HM, Wagner V, Bonadio WA, Glaeser PW, Losek JD, Walsh-Kelly CM et al. The effect of oral midazolam on anxiety of preschool children during laceration repair. Annals of Emergency Medicine 1990; 9:1006-1009.

(20) Hunt GS, Spencer MT. Etomidate and midazolam for procedural sedation: prospective trial. Annals of Emergency Medicine 2003; 42, 540.

(21) Ioannidis JP, Haidich AB, Pappa M, Pantazis N, Kokori SI, Tektonidou MG et al. Comparison of evidence of treatment effects in randomized and nonrandomized studies. JAMA 2001; 286:821-30.

(22) Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Controlled Clinical Trials 1996; 17:1-12.

(23) Juni P, Witschi A, Bloch R, Egger M. The hazards of scoring the quality of clinical trials for meta-analysis. JAMA 1999; 282:1054-60.

(24) Kanegaye JT, Favela JL, Acosta M, Bank DE. High-dose rectal midazolam for pediatric procedures: a randomized trial of sedative efficacy and agitation. Pediatric Emergency Care 2003; 5:329-336.

(25) Kennedy RM, Porter FL, Miller JP, Jaffe DM. Comparison of fentanyl/midazolam with ketamine/midazolam for pediatric orthopedic emergencies.[see comment]. Pediatrics 1998; 102:956-63.

(26) Kharasch SJ, Chand R, Kastner B, Bauchner H. Is ketamine the sedative of choice for closed fracture reduction in children? A randomized trial of

ketamine versus fentanyl/midazolam (Abstract). Pediatric Academic Society/Society of Pediatric Research Annual Meeting, May 2003.

(27) Kienstra AJ, Ward MA, Sasan F, Hunter JV, Morriss MC, Macias CG. Etomidate vs. pentobarbital for sedation of children for head and neck CT imaging (Abstract). Pediatric Academic Society/Society of Pediatric Research Annual Meeting, May 2003.

(28) Klein EJ, Diekema DS, Paris CA, Quan L, Cohen M, Seidel KD. A randomized, clinical trial of oral midazolam plus placebo versus oral midazolam plus oral transmucosal fentanyl for sedation during laceration repair. Pediatrics 2002; 109:894-7.

(29) Kunz R, Oxman DD. The unpredictability paradox: review of empirical comparisons of randomised and non-randomised clinical trials. British Medical Journal 1998; 317:1185-1190.

(30) Luhmann JD, Kennedy RM, Porter FL, Miller JP, Jaffe DM. A randomized clinical trial of continuous-flow nitrous oxide and midazolam for sedation of young children during laceration repair. Annals of Emergency Medicine 2001; 37:20-7.

(31) Luhmann JD, Schootman M, Voytas L, Luhmann SJ, Kennedy RM. A comparison of ketamine/midazolam and nitrous oxide/hematoma block for forearm fracture reduction in children (Abstract). Pediatric Academic Societies' Annual Meeting, May 2004.

(32) McGlone RG, Ranasinghe S, Durham S. An alternative to "brutacaine": a comparison of low dose intramuscular ketamine with intranasal midazolam in children before suturing. Journal of Accident & Emergency Medicine 1998; 15:231-6.

(33) Moher D, Cook D, Eastwood S,Olkin I,Rennie D,Stroup D. Improving the quality of reports of meta-analyses of randomized controlled trials: the QUOROM statement. Lancet 1999; 354:1896-1900.

(34) Moro-Sutherland DM, Algren JT, Louis PT, Kozinetz CA, Shook JE. Comparison of intravenous midazolam with pentobarbital for sedation for head computed tomography imaging. Academic Emergency Medicine 2000; 7:1370-5.

(35) O'Brien JF, Falk JL, Carey BE, Malone LC. Rectal thiopental compared with intramuscular meperidine, promethazine, and chlorpromazine for pediatric sedation. Annals of Emergency Medicine 1991; 20:644-647.

(36) Petrack EM, Marx CM, Wright MS. Intramuscular ketamine is superior to meperidine, promethazine, and chlorpromazine for pediatric emergency department sedation. Archives of Pediatrics & Adolescent Medicine 1996; 150:676-81.

(37) Qureshi FA, Mellis PT, McFadden MA. Efficacy of oral ketamine for providing sedation and analgesia to children requiring laceration repair. Pediatric Emergency Care 1995; 11:93-7.

(38) Roback MG, Wathen JD, Mackenzie T, Hurley D. Length of sedation with ketamine administered IV vs. IM in a PED. Annals of Emergency Medicine 2004; 11:488-489.

(39) Roth KR, Herr SM, Pitetti RD, Zucherbraun NS, Fine GF, King C. Comparison of etomidate and fentanyl with midazolam and fentanyl for sedation and analgesia during fracture in a pediatric ED (Abstract). Pediatric Academic Society/Society of Pediatric Research Annual Meeting, May 2004.

(40) Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. JAMA 1995; 273:408-12.

(41) Schutzman SA, Burg J, Liebelt E, Strafford M, Schechter N, Wisk M et al. Oral transmucosal fentanyl citrate for premedication of children undergoing laceration repair. Annals of Emergency Medicine 1994; 24:1059-64.

(42) Schutzman SA, Liebelt E, Wisk M, Burg J. Comparison of oral transmucosal fentanyl citrate and intramuscular meperidine, promethazine, and chlorpromazine for conscious sedation of children undergoing laceration repair. Annals of Emergency Medicine 1996; 28:385-90.

(43) Shane SA, Fuchs SM, Khine H. Efficacy of rectal midazolam for the sedation of preschool children undergoing laceration repair. Annals of Emergency Medicine 1994; 24:1065-73.

(44) Sherwin TS, Green SM, Khan A, Chapman DS, Dannenberg B. Does adjunctive midazolam reduce recovery agitation after ketamine sedation for pediatric procedures? A randomized, double-blind, placebo-controlled trial. Annals of Emergency Medicine 2000; 35:229-38.

(45) Taiwo B, Flowers M, Zoltie N. Reducing children's fear when undergoing painful procedures. Archives of Emergency Medicine 1992; 9(3):306-9.

(46) Terndrup TE, Dire DJ, Madden CM, Gavula D, Cantor RM. Comparison of intramuscular meperidine and promethazine with and without chlorpromazine: a randomized, prospective, double-blind trial. Annals of Emergency Medicine 1993; 22:206-11.

(47) Theroux MC, West DW, Corddry DH, Hyde PM, Bachrach SJ, Cronan KM et al. Efficacy of intranasal midazolam in facilitating suturing of lacerations in preschool children in the emergency department. Pediatrics 1993; 91:624-7.

(48) Wathen JE, Roback MG, Mackenzie T, Bothner JP. Does midazolam alter the clinical effects of intravenous ketamine sedation in children? A double-blind, randomized, controlled, emergency department trial. Annals of Emergency Medicine 2000; 36:579-88.

(49) Younge PA, Kendall JM. Sedation for children requiring wound repair: a randomised controlled double blind comparison of oral midazolam and oral ketamine. Emergency Medicine Journal 2001; 18:30-3.

Chapter Three: Summary of results of systematic review

Section 3.1: Introduction to results of systematic review

3.1.1 Summary of search and selection of studies

35 randomized controlled clinical trials that met the inclusion criteria from the literature searches on sedation for painful or anxiety provoking procedures in paediatric emergency departments (EDs). To be included, the studies were required to use some outcome measure that evaluated efficacy, time of sedation and/or adverse effects. The search spanned all literature cited in MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL) and Dissertation Abstracts. It also included searches for unpublished articles from pharmaceutical companies, experts and trialists, and conference proceedings. Results of this search and the reasons for exclusion of studies were detailed in Chapter 2. The populations, interventions, outcome measures and quality of each included study were also summarized in Chapter 2. This chapter summarizes the evidence for the use of the therapeutic agents described in Chapter 2.

3.1.2 Methods of Data Analysis

The data from the selected studies were analysed qualitatively and quantitatively, where appropriate.

The quantitative analysis was completed as per the approach outlined in the original Cochrane Protocol.(7) Meta-analysis was performed using RevMan 4.2.7 (The Cochrane Collaboration 2004). Results were pooled when there were at least two randomized controlled trials (RCTs) that evaluated the efficacy of the same drug, dose and route using the same outcome measures. For continuous variables, a mean difference (MD) was calculated for each study; a weighted MD (WMD) was calculated when results from different studies were combined. For dichotomous variables, odds ratio (OR) and/or relative risk (RR) were calculated for individual studies with available data. All similar studies were combined using the appropriate measure and a 95% confidence interval (95% CI) was calculated. A random effects model was used for pooling. For pooled effects, heterogeneity was tested using the chi-squared and I-squared tests for heterogeneity. For the chi-square, $p < 0.1$ was considered statistically significant; for I-squared, a value greater than 50% was considered substantial heterogeneity. Heterogeneity is thought to detect fundamental differences between studies, indicating that their results should not be combined or, if combined, the causes of heterogeneity should be explored and the results interpreted with caution.

Qualitative analyses were performed on the individual studies, grouped according to drug class. Efficacy measures (e.g., sedation, pain, and satisfaction scores), times (e.g., time to sedation, duration of sedation) and adverse effects were all analyzed for comparisons performed between any sedative or dissociative agent versus any other sedative or dissociative agent.

Despite the large number of RCTs identified by the search methods, there were remarkably few that evaluated the same medications administered via the same routes. There were only three comparisons, involving seven studies, which examined the same drug type and route. Three studies compared oral (PO) benzodiazepines to placebo(9;14;35), two studies evaluated intravenous (IV) ketamine with and without midazolam(33;38), and two of the studies contrasted inhaled nitrous oxide (N_2O) to placebo.(4;10) Section two of this chapter includes a description of the outcome measures that are common within these subgroups of studies. Further details of these studies can be found in the relevant sections that are organized according to type of sedative used.

Apart from these seven studies, there were many other trials that compared the same groups of drugs; however, they were all combined with additional study drugs therefore statistical pooling of data was deemed to be inappropriate. For example, Kennedy et al(18) compared IV ketamine with midazolam to IV fentanyl plus midazolam, and Kharasch et al(19) contrasted IV ketamine with IV fentanyl plus midazolam. Superficially, these two studies appear similar, aside from the addition of midazolam to the ketamine arm of the study by Kennedy. On closer inspection, however, in Kennedy's protocol, all subjects initially received midazolam until the speech became slurred or the eyes glassy or a maximum first dose of 0.3 milligrams per kilogram (mg/kg) was reached. This indicates that the midazolam played a clinically important role in the sedation, and thus it is not reasonable to combine the two studies for purposes of meta-analysis.

Likewise, there was variability in the measures of efficacy that were used in the included studies, and often they were interpreted and/or reported in different ways. Variable sedation scores were used in the RCTs including: a four-point scale(25), a five-point scale(1;12;17;27;39), a six-point scale(13;24), a 10-point scale(15) and a 10 or 10.2 centimetre VAS.(1;36) Most of the 25 other studies used a combination of pain scores, anxiety scores and distress scores, along with satisfaction rates and/or success of procedures.

In addition, there were 11 different types of times recorded in these 35 RCTs. These can be grouped into five major groups: onset of sedation, procedure time, sedation time, recovery time and time to discharge.(Table 3.17)

Section 3.2: Quantitative Results

3.2.1 Oral benzodiazepines vs. placebo (t=3, n=195)

Three trials evaluated benzodiazepines versus placebo(9;14;35) using a measure of anxiety (Table 3.1), however they used different methods of reporting the score. Individually and pooled the trials showed significantly less anxiety with the use of benzodiazepines over placebo (Figure 3.1) (total RR: 1.98; 95% CI: 1.50 to 2.60). The tests for heterogeneity were significant ($P=0.004$; $I^2=81.6\%$), indicating that this result should be interpreted with caution because the summary estimate may not reflect the true treatment effect. Further details of these studies can be found below in Section 3.3.4.

3.2.2 IV Ketamine with and without midazolam (t=2, n=370)

Intravenous ketamine was compared with and without midazolam in two studies.(33;38) The outcome measures (Table 3.2) were different for the two studies except for somewhat similar measurements of time (time to discharge(33); total sedation time(38)), where there was no significant difference identified. Results on the details of the other outcome measures are discussed in Section 3.3.2.1.

3.2.3 Nitrous oxide (N_2O) vs. placebo (oxygen) (t=2, n=51)

Gamis(10) and Burton(4) both used the Children's Hospital of Eastern Ontario Pain Score (CHEOPS) tool (lower score equals better sedation, Appendix 3.1) to compare N_2O to oxygen (O_2) (Table 3.3). The combined results favoured N_2O over O_2 (WMD -3.55; 95% CI: –4.91 to –2.19; Figure 3.2). However, the test for heterogeneity was significant ($I^2=73\%$; Chi-squared = 7.49; $p=0.02$). When studies were grouped by age (<8 years old), the results remained significant and the heterogeneity remained (Figure 3.2).

Section 3.3: Qualitative Results

Meta-analyses were limited because of the lack of similar comparisons across trials. Evidence tables were used to summarize the characteristics and findings of individual studies. Tables 3.4 to 3.16 describe the efficacy outcomes for individual studies, grouped by comparison. The key measures of efficacy listed include sedation, pain, anxiety, satisfaction (of the parent, nurse and/or doctor), distress, and success rates of the procedure. Some authors(34) argue that systematic reviews should not include "surrogate markers" of pain, due to poor concordance between patients' and practitioners' assessments of pain. These additional outcome measures were included in this systematic review in an attempt to gain a broader perspective on all aspects of sedation, including the impact on the caregivers and health care workers. Table 3.17 describes the types of times studied and the results for individual studies. Median drug half-life was not correlated with length of stay based on single drug comparisons ($r = 0.02$). Finally, Tables 3.18 to 3.23 describe the adverse effects for individual studies, grouped by drug type. The results are discussed below, organized by sedative group.

3.3.1 Opiates vs. other agents (t=8, n=627; 1 trial (n=42) used in both sections)

3.3.1.1 Opiates vs. meperidine, promethazine and chlorpromazine (MPC) (t=3, n=123)

Three trials compared an opiate to intramuscular (IM) MPC (Table 3.4). One study found no significant difference between opiates and IM MPC with respect to sedation, while another study found a statistically significant difference favouring MPC over fentanyl. None of the studies that examined pain (n=3) and anxiety (n=2) found a statistically significant difference between opiates and MPC.

Hart et al noted the prolonged duration of action with MPC compared to fentanyl with or without midazolam (Table 3.17). Only one study reported on adverse effects(31) and found a high overall rate (75% with transmucosal fentanyl; 68% with MPC); however, infrequent desaturations in both groups (Table 3.18).

3.3.1.2 Opiates plus another sedative agent vs. other agents (t=6, n=546)

Six studies compared opiates in conjunction with another sedating agent (Table 3.5). Most of these are discussed in greater detail under the headings of the sedating agent. Kennedy(18) found that patients who received the traditional combination of fentanyl with midazolam had significantly more distress than those receiving ketamine (also with small dose of midazolam). While this difference is statistically significant ($p<0.0001$), the clinical relevance is questionable as this scale ranges from 0 to 23.5 (difference: 1.08+/-1.12 vs. 2.7+/- 2.16).

3.3.2 Ketamine vs. other agents (t=11, n=1137)

3.3.2.1 Ketamine vs. benzodiazepines (t=4, n=482)

Four trials examined ketamine compared with benzodiazepines (Table 3.6). In the two trials that compared ketamine and midazolam, ketamine was found to be superior in terms of sedation score(1;39) and parent satisfaction(1). Intravenous ketamine was used with and without midazolam by two study groups(33;38), as mentioned in Section 3.2.2. These studies hypothesized that midazolam may reduce emergence phenomena that occurs with ketamine. It would appear that there is little evidence to suggest that adding a benzodiazepine to ketamine improves outcomes for painful procedures.

3.3.2.2 Ketamine vs. other agents (t=7, n=655)

Six studies compared ketamine to other sedatives, one compared IM to IV ketamine (Table 3.7). Ketamine was repeatedly found to provide excellent sedation based on the sedation, pain and anxiety scores reported in each study.(11;18;19;26;27) The drawback to ketamine was that it resulted in longer recovery times (mean difference: 33.4 minutes) when compared with other agents such as propofol.(11)

3.3.3 MPC vs. other sedatives (t=6, n=266)

Six studies compared MPC with other sedatives (Table 3.8). Three comparisons with opiates(3;12;31) and one comparison with ketamine(26) are reviewed under the relevant sections. In summary, MPC was found to provide no significant improvement in sedation over thiopental, opiates plus midazolam, or fentanyl in isolation, when evaluated using the validated CHEOPS score. MPC consistently took longer to wear off than all medications studied (Table 3.17), and in one study(26) was found inferior to ketamine in terms of relieving distress. To a large degree this comparison is important for historical reasons only, since the combination treatment is rarely used in clinical care in the emergency department.

3.3.4 Benzodiazepines vs. other agents (t=25, n=2140)

3.3.4.1 Benzodiazepines vs. placebo or standard care (t=6, n=492)

Six studies compared benzodiazepines with placebo or standard care (Table 3.9). Fatovich(9) (n=107), Hennes(15) (n= 55) and Taiwo(35) (n=33) contrasted anxiety scores of patients who received oral midazolam versus those who were given placebo, as described in section 3.2.1. Individually, all three studies found a statistically significant reduction in anxiety using midazolam.

While patient and parental assessment of anxiety may differ, both patient(9;14;35) and parental(9;32;37) anxiety were significantly lower using midazolam compared to placebo. The two studies that measured sedation found statistically significant benefit of midazolam over placebo/no treatment. While one study found greater parent satisfaction for midazolam vs. placebo(37). The interpretation of the data from Luhmann(22) is challenging, as it is not clear which p-values result from which comparisons. While the use of midazolam delays departure from the ED (59 vs. 42 minutes(32)), and results in prolonged recovery times (30 vs. 20 minutes(22)) (Table 3.17), these delays are of questionable clinical importance, given that the alternative was placebo.

3.3.4.2 Benzodiazepines vs. benzodiazepines (t=4, n=298)

Four studies compared two or more benzodiazepines of different doses or routes (Table 3.10). These data could potentially be combined to determine an optimal dose and route; however, the outcome measures used were not comparable. In general, the studies could be categorized as high dose vs. low dose.

Two studies compared high vs. low doses: one (which used the oral route) found no significant difference in pain or anxiety(6), and the other, in which midazolam was administered rectally, found 1.0mg/kg achieved better sedation than 0.5mg/kg.(17) Times to sedation(6) and recovery(17) appeared similar, but discharge times were discrepant. Kanegaye(17) found no significant difference, but Davies(6) reported that the 9 subjects that received 0.2mg/kg of oral midazolam were discharged within a mean time of 49 minutes and the 41 who received 0.5 mg/kg were discharged at 60 minutes (Table 3.17). These trends are interesting and hypothesis generating; however, given the range of doses (0.2-1.0 mg/kg), the routes (IN, PO, PR), and the agents (midazolam and diazepam), more work is needed to define the dose of benzodiazepine required for effective and safe sedation in children.

3.3.4.3 Benzodiazepines vs. other agents (t=8, n=702)

Eight trials were identified that compared benzodiazepines to "other" agents (Table 3.11). Five studies reported on sedation and overall there was either no significant difference between treatment groups, or midazolam was significantly less effective than pentobarbital, ketamine, propofol and etomidate. Times (Table 3.17) were found to be prolonged with midazolam in 5 studies(1;13;20;29;39). The other 3 studies found no significant difference from placebo(33) or ketamine(38), or did not report times.(24)

See other subheadings for details of studies comparing benzodiazepines with ketamine(1;33;38;39), propofol(13), and etomidate.(15;29)

3.3.4.4 Benzodiazepines combined with other sedatives or analgesics (t=7, n=648)

These combinations include opiates(12;18;19;21;29), ketamine(18), nitrous oxide(23) and propofol(11) and are all discussed under the heading of another sedative/analgesic (Table 3.12).

3.3.5 N_2O vs. other agents (t=4, n=370)

Four studies compared N_2O to placebo (oxygen) or other sedating regimens (Table 3.13). N_2O performed significantly better than placebo as well as midazolam in terms of pain(4;10), and anxiety.(14) Combined with a hematoma block, N_2O provided better pain control and less distress than ketamine plus midazolam.(23)

Two studies(4;10) compared nitrous oxide to placebo. Gamis(10) (n = 35) reported favourable results for children older than eight years who received N_2O; however, not in those under 8. Burton et al(4) reported favourable results with N_2O for their study sample, which included children aged 2 to 7 years.

Two abstracts by Luhmann(22;23) described the same research, each providing slightly different details. Luhmann and his colleagues used another unique measure of efficacy, the "Procedure Behavioural Checklist: PBCL" which was not referenced or explained. Attempts to contact the authors were unsuccessful.

3.3.6 Barbiturates vs. other agents (t=3, n=141)

See other subheadings for comparisons of barbiturates to benzodiazepines(24), etomidate(20) and MPC.(25) (Table 3.14)

3.3.7 Propofol vs. other agents (t=2, n=202)

Propofol was compared to midazolam in two studies (Table 3.15). Havel(13) measured sedation using the Ramsay sedation score (Appendix 3.3) and found no significant difference between propofol IV and midazolam IV. Godambe(11) compared propofol plus fentanyl IV to ketamine plus midazolam and found significantly more distress with the propofol/fentanyl combination; however, there were no significant differences for pain, MD/RN satisfaction, and success rates.

3.3.8 Etomidate vs. other agents (t=3, n=133)

There is limited data on the use of etomidate for procedural sedation in children. Three studies of this agent provide conflicting conclusions (Table 3.16). Upon initial inspection it appears that etomidate provides sedation more quickly and with shorter recovery times than either midazolam or the barbiturate comparison.(15;20;29) (Table 3.17) It is possible that the different results are a consequence of different dosing regimens as well as varied, undefined outcome measures.

Section 3.4: Adverse Effects

3.4.1 Frequency of adverse effects

In order of decreasing frequency, adverse effects occurred in 14% of patients who received MPC, 12% of patients who received some opiate in their sedation regimen, 11% of those who received propofol, 9% of those who received nitrous oxide or etomidate, 8% of those who received benzodiazepines, 7% of those who received barbiturates and 5% of those who received ketamine (Figure 3.4). There was no significant difference between these adverse event rates (χ^2 = 6.173; df = 7; p = 0.52). The average adverse event rate of all studies was 9.4%.

3.4.2 Types of adverse effects reported

The following is a summary of the wide variety of adverse effects reported within the relevant trials:

- Eight studies reported the "overall" adverse event rate.(1;18;21;25;27;30-32)

- 21 studies reported some form of respiratory side effects, including: respiratory depression(12), desaturation to less than 95%(1;3;4;13;19;21;24;25;28;30;31;33;37), less than 93%(21) and/or less than 90%.(1;11;12;18;36;39) Other respiratory effects included hypoxemia(38), hypercarbia(38), apnoea(4;19;37) and/or stridor/laryngospasm.(1;18;19;27;38)

- Psychological effects were reported in 21 studies, including emergence reactions(1;12;18;19), dysphoric reactions(1;11;13;18;19;27;38) and hallucinations.(39) Recovery agitation(22;33), agitation(5;13;31), inconsolable agitation(32) and inconsolability(8;33) were listed, as well as crying(30), paradoxical hyperactivity(36;39), sleeping difficulties(6), nightmares(26) and over-sedation.(4;38) Havel (13) described patients who were "sedated during the 24-hour post-procedure" time; drowsiness was reported by five author groups(8;10;22;31;39) and one group(37) reported delayed lethargy.

- Vomiting was a reported side effect in 15 studies. (1;4;10;18;21;22;26-28;30;31;33;36-38)

- Central nervous system disturbances including headache(27), vertigo(22), ataxia(37), unsteady gait(36), dizziness(4;22) and random movements(1;18) were also reported variably.

- Other complications that were reported included nausea/gagging(39), abdominal pain(30), pruritis(21;30), "administration complications"(31) and pain with injection.(5;13;28)

3.4.3 Adverse effects with opiates

Adverse effects that were reported in the studies comparing opiates with other sedatives included haemoglobin oxygen desaturation, hypercarbia, apnoea, laryngospasm/stridor, vomiting, agitation, emergency reactions, hypotension, pruritis and pain on injection (Table 3.18). Three of the seven studies that reported on oxygen saturation found that opiates significantly reduced oxygen saturation compared to the other treatment groups. Two of four studies reported a significantly higher incidence of vomiting among the opiate group. None of the studies that evaluated stridor/laryngospasm, apnoea, or dysphoric reactions found a significant difference between treatment groups.

3.4.4 Adverse effects with ketamine

Adverse effects that were reported with ketamine included: oxygen desaturation, stridor/laryngospasm, apnoea, vomiting, dysphoric reactions, random movements, and pain on injection. None of these were found to be statistically more common with ketamine (Table 3.19) than comparative agents.

Three of the six studies that compared ketamine to a number of other drugs found a higher incidence of dysphoric reactions in the ketamine group; however, the difference between groups was not statistically significant. In one of the six studies, there were significantly fewer rather than more dysphoric reactions for ketamine compared to midazolam.(39) In three of six studies that reported on desaturations, ketamine was found to cause significantly fewer oxygen desaturations compared to fentanyl IV(18;19) and propofol.(11)

3.4.5 Adverse effects with MPC

Adverse effects reported with MPC included oxygen desaturation, hypercarbia, pruritis, agitation and vomiting. These did not occur statistically more frequently with MPC than other agents in any of these studies (data not shown).

3.4.6 Adverse effects with benzodiazepines

The adverse effects that occurred in the studies evaluating benzodiazepines included: apnoea, stridor/laryngospasm, hyper-carbia, hypoxia, hypotension, drowsiness or over-sedation, vomiting, pain with injection, crying, dysphoric reactions and unsteady gait (Table 3.20). Of all these adverse effects, very few were found to occur significantly more or less commonly with benzodiazepines than the comparison agents. Overall, there were few significant differences in the rate of adverse effects for 1794 patients sedated using benzodiazepines and 1869 patients using some other form of sedation.

3.4.7 Adverse effects with N_2O

Vomiting was reported as a side effect in three N_2O studies; however, the difference between N_2O and oxygen was statistically significant in only one of these.(22) Dizziness, crying, and hypoxemia were each reported in one study. Dizziness(4) (95% CI [0.01, 0.46]) and crying(22) (RD = 0.10; 95% CI [0.01, 0.19]) were more common with N_2O (Table 3.21). Hypoxemia did not occur in any patient in either study group.(4)

3.4.8 Adverse effects with barbiturates

The only adverse effect reported in the studies on barbiturates was desaturation, and those two studies did not show any significant difference compared to benzodiazepines(25) and MPC.(25) (Table 3.22).

3.4.9 Adverse effects with propofol

Adverse effects that were reported with propofol included: oxygen desaturation, stridor/laryngospasm, apnoea, vomiting, dysphoric reactions, low blood pressure, over sedation, and pain with injection (Table 3.23). The only one that occurred significantly more often with propofol (combined with an opiate) was oxygen desaturation when compared to ketamine.(11)

3.4.10 Adverse effects with etomidate

The adverse effects reported in the studies evaluating etomidate included myoclonus, pain with injection, airway obstruction, hypoxia, vomiting, and apnoea (Table 3.24). The effects that occurred significantly more with etomidate included: airway obstruction requiring repositioning (RD=-0.31; 95%CI: -0.54, -0.08), motion artefact (RD=-0.30; 95%CI: -0.52, -0.08) and pain with injection (RD = 0.29; 95% CI: 0.08, 0.49).

Section 3.5: Discussion

Quantitative and qualitative analysis of systematic review data both contribute valuable information to healthcare decision-making. Quantitative analysis (meta-analysis) is performed to combine the results of two or more studies that report similar study designs, populations, interventions, controls and outcomes. The goal is to achieve a more precise estimate and greater statistical power to detect the true effect of an intervention. This is particularly helpful when different investigators have reported conflicting results on the same subject.

There are frequently barriers to quantitative analysis. Study design may be different; moreover, RCTs may not have been performed. The RCTs included in a systematic review may be too disparate in terms of the population studied, the intervention used or the outcome(s) measured. Qualitative systematic reviews are then performed, with the aim of summarizing the existing data, aiding understanding of discrepancies in the available evidence, and helping to guide future direction of research on the topic in question. This chapter includes both quantitative and qualitative analyses.

3.5.1 Quantitative analysis

Several quantitative analyses were performed on studies included in this systematic review that compared the same class of drugs using the same outcome measure. The three studies that contrasted oral benzodiazepines to placebo(9;14;35) found less anxiety with midazolam (Figure 3.1). Two studies(4;10) reported improved CHEOPS scores for patients who received N_2O over those receiving placebo. Pooling these data did not result in different conclusions than had been reached by the individual studies, and served only to reinforce their conclusions

3.5.2 Qualitative analysis

3.5.2.1 The most efficacious medication

There are a large variety of sedatives, analgesics and combinations that have been used for the purposes of reducing pain and/or anxiety in children undergoing painful and anxiety provoking procedures. When evaluating the efficacy of a sedative, it is important not only to use a validated score but also one that is clinically relevant. Valid sedation scores were used in 10 studies, but pain scores, anxiety scores, distress scores, satisfaction rates and/or success of procedures were recorded in the other studies. While these may appear to be interesting and useful outcomes, this is only the case if they have been psychometrically tested. For example, many of the studies chose the CHEOPS scale(3;4;10;19;21;30;31), a valid measure that is designed to evaluate postoperative pain in children. However, it is not clear whether this tool accurately reflects the efficacy of a sedative in the acute care setting.

It may be argued that the ultimate goal of a sedative is to reduce the distress of the patient, as well as the caregivers and healthcare workers. Psychologists designed and revised "The Observational Score of Behavioural Distress" (Appendix 3.2) to assess children's distress during painful medical procedures. This is a complex scoring system that may not be practical to use in the emergency setting.

Another problem with the measurement of efficacy in these studies is that while similar scoring systems may have been used, they are recorded in unique ways. Not only does this preclude consolidating the data in meta-analysis, it makes it difficult to interpret data that is reported in different ways, as occurred in the six studies that compared benzodiazepines to placebo using different scores intended to evaluate anxiety.(9;14;22;32;35;37)

One finding in this systematic review was that every study that compared a sedative and/or analgesic to placebo concluded that the drug evaluated provided superior sedation over the placebo.(4;6;9;14;27;32;35;37) Realizing that using any of these drugs is better than placebo, restraint (often referred to as "Brutane") or no treatment is an excellent first step to developing an approach to children with these problems. Unfortunately, this doesn't help clinicians decide which is the best drug and more drug-to-drug comparisons are required.

3.5.2.2 The sedation regimen with the fastest times

There were many different time measurements reported in the trials included in this systematic review. We grouped these under the following headings: onset of sedation, procedure time, sedation time, recovery time and time before discharge. Times to discharge were recorded by many studies with no consistent results (Figure 3.3). There are many factors that may have influenced time to discharge, directly or indirectly, and consequently interpretation of statistically significant findings must be performed while keeping these in mind.

Potential confounders include: blinding (as doctors are likely to observe patients in the ED for longer if they know that a potential respiratory depressant has been administered), type and consequent duration of procedure, ED volumes and pressures (which vary hour to hour and influence both the times to start procedure from the time of admission as well as the time to discharge), staff availability, definition of recovery and whether or not predefined discharge criteria were applied, and personal bias and comfort level of the attending physician. The study by Hunt(15) exemplifies the impact of other factors on times. These authors report the mean length of sedation was 12.84 +/-9.39 minutes for etomidate and the mean time to disposition was 119.53 +/- 71.00 minutes. It is possible that the prolonged ED time included a protracted recovery period.

Perhaps the most practically relevant time recorded by investigators is the time to discharge, since the time a child remains in the ED is important to the patient, caregivers, healthcare workers and policy makers. There is clearly important variation in the times to discharge (Figure 3.3), with little or no consistent pattern. Similar graphs are seen when other subgroups of times are plotted. Once again, this reflects the lack of consistent definitions of what specific time period was measured, as well as the other variables such as how long the procedure took to complete.

Keeping these limitations in mind, it is interesting to note that the sedatives that had the shortest times to discharge and/or duration of sedation were the ones known to have the fastest onset (nitrous oxide(4), etomidate(29), propofol(11;13)) with short durations of action. Future research in this area must define the times carefully and validate this hypothesis.

3.5.2.3 Sedating with the fewest adverse effects

It is difficult to compare the studies with respect to adverse effects, as there was great variability on what was reported, and in what way. For example, some studies defined hypoxia as oxygen saturation less than 95%(3) and others as less than 90%(39) and others included both options.(1) Compared to other agents, ketamine appeared to have the fewest side effects. Moreover and not surprisingly, MPC (an older combination agent) appeared to have the highest proportion of side effects. Despite concern regarding emergence phenomena as an adverse event associated with ketamine use, the studies included in this review failed to identify more frequent emergence phenomena for ketamine than other sedatives. This may be because the sample sizes were not large enough to evaluate rare adverse outcomes, and may be influenced by the historical finding that children do not seem to suffer this complication as frequently as adults. Alternatively, non-systematic reporting of adverse events may have had a role to play in these results. These general observations are consistent with clinical practice, where the use of some sedative combinations has been strongly discouraged.(2)

Reporting an overall percentage of events doesn't provide any indication of the severity of these adverse effects, nor does it compare the relative severity between agents. The studies do not specify how rigorously the adverse effects were measured, and this is an important consideration. There are many unanswered questions when looking at the adverse effects, including whether all the researchers searched for the same adverse effects with the same rigour in all treatment groups. It is difficult to know if the authors only reported adverse effects that they saw, or whether they searched for adverse effects in a systematic fashion such as routine measurement of vital signs, questioning of providers, or checklist completion. Alternatively, if there were no adverse effects, investigators may have reported these as zero or not reported them at all. Other useful information that is inconsistently included in the articles is whether adverse effects were reported per patient or by total number of events.

There is a growing body of literature suggesting that RCTs are inadequately powered to examine adverse effects because of their limited sample size and short follow-up period.(16) An excellent recent example is the removal of the anti-inflammatory Vioxx (rofecoxib) from the musculo-skeletal armamentarium due to cardiovascular adverse events.(40) The original trials were underpowered to identify these adverse events. While other study designs may not be ideal for studying treatment effects, harmful effects may be better evaluated using a combination of other resources such as licensing bodies that control medications distributed for public use.

Section 3.6: Summary

The ideal agent for painful or anxiety provoking procedures in the acute care setting should be easy to administer, have a rapid onset of action, be free of major and minor side effects, reverse easily, and be predictably effective. Unfortunately, none of the agents currently available, nor those reported in this review, have all of these properties. The RCTs in this systematic review, separately or combined, did not demonstrate one particular drug or combination of drugs to be the most effective at reducing pain and anxiety, with an onset of action in a timely fashion, with the least adverse effects. This may be more reflective of the varied designs and objectives of the studies rather than the true lack of difference between the medications. The challenge of interpreting these data lies in the complexity of evaluating comparisons between so many types and subtypes of medications using such a variety of outcome measures.

Although we were unable to pool results because of great variation in comparisons across the included trials, this review does provide important information on adverse effects, time of onset, and clinical efficacy. Moreover, these results reinforce the need for physicians to use judgment obtained from understanding the pharmacology as well as experience with the different medications when choosing their agent on an individualized basis. For example, a child who requires sedation for a short, painless but anxiety provoking procedure would benefit from sedation with a pure sedative (no analgesia required) that is easy to administer and relatively short acting, such as an ultra-short acting barbiturate (e.g. PR thiopental(25)). On the other hand, for a child who will be undergoing a prolonged and painful procedure such as repair of a complicated laceration, a longer acting drug that consistently provides both sedation and analgesia, such as IV ketamine.(18) For relatively short but painful procedures, short-acting relatively new medications such as propofol or etomidate combined with a short acting opiate (e.g. fentanyl), may work best.(11;29)

Chapter four of this thesis will outline important considerations for designing an RCT to determine the optimum regimen of medications to provide sedation with or without analgesia to children undergoing painful or anxiety-provoking procedures in the ED.

Tables

Notes:

1. Abbreviations: refer to list on page xv.
2. In reporting effect sizes, we attempted to use a measure of effect such as RR (with 95% CI) for dichotomous variables and MD (with 95% CI) for continuous variables. In the cases where insufficient data were available, we attempted imputation wherever possible or provided the available statistical test from the manuscript.
3. Sedation measures include sedation, activity, behaviour, effort, cry, motion and/or struggle scales and scores.
4. Bolded authors = published in abstract only.
5. Mixed procedures include: orthopaedic, lacerations, burns, dental, and/or surgical procedures.
6. * = 95% CI does not include zero.

Table 3.1: Outcomes of PO benzodiazepines vs. placebo

Study	**Outcome measure**	**Results**	**Effect (95%CI)**
Hennes 1990	Improvement in anxiety score >=2/4points	Midazolam: 21/30 Placebo: 3/25	RR=5.83 (1.97, 17.30) favours midazolam
Taiwo 1992	Any improvement in anxiety score /4	Midazolam: 10/16 Placebo: 3/17	RR=3.54 (1.19, 10.58) favours midazolam
Fatovich 1995	Anxiety score 3 or 4/4 (4=most anxious)	Midazolam: 10/57 Placebo: 21/50	RR=1.42 (1.09, 1.85) favours midazolam

Table 3.2: Outcomes of IV Ketamine with and without midazolam

Study ID	**Outcome measure**	**Results**	**Effect (95%CI)**
Wathen 2000	OSBDR	Midazolam: mean=0.53, SD=0.89 Control: mean=0.64, SD=1.05	MD=-0.12 (-0.35, 0.11)
Sherwin 2000	Recovery agitation 100mm VAS by MD	Midazolam: median 4 (IQR=2-19) Placebo: median 5 (IQR=3-14)	MD=1.30 (-4.77, 7.37)

Table 3.3: Outcomes of nitrous oxide (N_2O) vs. placebo

Study ID	Outcome measure	Results	Effect (95%CI)
Gamis 1989	CHEOPS age 2-7 years	N_2O mean=8.5, SD=2.9 O_2 mean=10.1; SD=2.8	MD=-1.60 (-4.04, 0.84)
	CHEOPS age >= 8 years	N_2O mean=5.6, SD=2.6 O_2 mean=7.6, SD=2.6	MD=-2.00 (-4.91, 0.91)
Burton 1998	CHEOPS (age 2-7 years)	N_2O median=1, range=0-6 O_2 median = 8, range=2-10	MD=-5.56 (-5.53, -2.45) favours N_2O

Table 3.4: Outcomes of opiates vs. meperidine, promethazine and chlorpromazine (MPC)

Author/year Age range Procedures	Opiate (n)	MPC IM (n)	Key Measures	Effect (95%CI)
Hart 1997 2-8 years Mixed	Fentanyl + midazolam IV (n=13) vs. fentanyl IV (n=20)	n=9	Sedation Pain Anxiety	NS: MD not estimatable NS: MD not estimatable NS: MD not estimatable
Schutzman 1996 3-8 years Laceration	Fentanyl TM (n=19)	n=20	Sedation Pain	MD not estimatable; favours MPC NS: MD not estimatable
Bates 1994 1-4 years Laceration	Sufentanil IN + midazolam IN (n=19)	n=23	Pain Anxiety	NS: MD not estimatable NS: MD not estimatable

Table 3.5: Outcomes of opiates vs. other agents

Author/year Age range Procedure	**Opiate (n)**	**Control (n)**	**Key Measures**	**Effect (95%CI)**
Godambe 2003 3.1-16.3 years Orthopaedic	Fentanyl + propofol IV (n=59)	Ketamine + midazolam IV (n=54)	Distress RN/MD satisfaction	MD=-0.20 (-0.39, -0.01) favours ketamine/ midazolam RN MD=0.10 (-0.04, 0.24); MD MD=0.08 (-0.05, 0.21)
Roth 2004 2-8 years Orthopaedic	Fentanyl + midazolam IV (n=16)	Etomidate IV (mean dose: 0.23 mg/kg) + fentanyl IV (n=21)	Distress	MD= –2.77 (-6.44, 0.90)
Hart 1997 2-8 years Mixed	Fentanyl + midazolam IV (n=13) vs. fentanyl IV (n=20)	MPC IM (n=9)	Pain Sedation Anxiety	NS: MD not estimatable NS: MD not estimatable NS: MD not estimatable
Kharasch 2000 3-13 years Orthopaedic	Fentanyl + midazolam IV (n=22)	Ketamine IV (n=21)	Pain	MD=-2.20 (-3.61, -0.79) favours fentanyl/midazolam
Kennedy 1998 5 to 15 years Orthopaedic	Fentanyl + midazolam IV (n=130)	Ketamine + midazolam IV (n=130)	Distress	MD=-1.62 (-2.04, -1.20) favours ketamine
Klein 2002 2-8 years Laceration	Fentanyl TM (n=28)	Placebo (n=23)	Pain Parent satisfaction	MD 0.60 (-0.97, 2.17) RR 0.85 (0.64, 1.14)

Table 3.6: Outcomes of ketamine vs. benzodiazepines

Author/year Age range Procedure	Ketamine (n)	Benzo (n)	Key Measures	Effect (95%CI)
Wathen 2000 0.5-16 years Mixed	Ketamine IV (n=129)	Ketamine + midazolam IV (n=137)	Distress	MD=-0.12 (-0.35, 0.11)
			MD/parent satisfaction	MD RR=0.97 (0.89, 1.06); Parent RR=0.92 (0.83, 1.01)
Sherwin 2000 1-15 years Mixed	Ketamine IV (n=51)	Ketamine + midazolam IV (n=53)	No efficacy outcomes reported	
Acworth 2001 0.5-12 years Mixed	Ketamine + midazolam IV (n=27)	Midazolam IN (n=26)	Sedation	MD=-2.00 (-2.89, -1.11) favours Ketamine
			Parent satisfaction	RR=1.41 (1.04, 1.91) favours Ketamine
			MD satisfaction	RR=0.20 (0.01, 3.97)
Younge 2000 1-7 years Laceration	Ketamine PO (n=30)	Midazolam PO (n=29)	Sedation	p=0.039: MD not estimatable; favours Ketamine
			Anxiety	NS: MD not estimatable

Table 3.7: Outcomes of ketamine vs. other agents

Author/year Age range Procedure	Ketamine (n)	Control (n)	Key Measures	Effect (95%CI)
Kharasch 2000 3-13 years Orthopaedic	Ketamine IV (n= 21)	Fentanyl + midazolam IV (n=22)	Pain	MD=-2.2 (-3.61, -0.79) favours fentanyl/midazolam
Petrack 1996 0.5-6 years Mixed	Ketamine IM (n=15)	MPC IM (n=12)	Distress Caregiver satisfaction MD satisfaction	MD –7.10 (-12.48, -1.72) favours MPC RR=1.23 (0.80, 1.89) RR=0.42 (0.21, 0.81) favours ketamine
Kennedy 1998 5 to 15 years Orthopaedic	Ketamine + midazolam IV (n=130)	Fentanyl + midazolam IV (n=130)	Distress	MD=-1.62 (-2.04, -1.20) favours fentanyl
Luhmann 2004 4-18 years Orthopaedic	Ketamine + midazolam IV (n=55)	N_2O + hematoma block (n=47)	Distress Pain MD satisfaction	MD=-1.61 (-1.81, -1.41) favours N_2O p=0.046: MD not estimatable; favours N_2O MD=7.00 (-4.8, 18.80)
Godambe 2003 3.1-16.3 years Orthopaedic	Ketamine + midazolam IV (n=54)	Fentanyl + propofol IV (n=59)	Distress RN/MD satisfaction	MD=-0.20 (-0.39, -0.01) favours propofol/fentanyl RN MD=0.10 (-0.04, 0.24); MD MD=0.08 (-0.05, 0.21)
Qureshi 1995 1-7 years Laceration	Ketamine PO (n=15)	Placebo (n=15)	Sedation	MD=-0.94 (-1.83, -0.05) favours ketamine
Roback 2002 5-16 years Orthopaedic	Ketamine IV (n=39)	Ketamine IM (n=41)	Pain Parent satisfaction	NS: MD not estimatable NS: MD not estimatable

Table 3.8: Outcomes of meperidine, promethazine and chlorpromazine (MPC) vs. other agents

Author/year Age range Procedure	MPC IM (n)	Control (n)	Key Measures	Effect (95%CI)
Hart 1997 2-8 years Mixed	n=9	Fentanyl + midazolam IV (n=13) vs. fentanyl IV (n=20)	Sedation Pain Anxiety	NS: MD not estimatable NS: MD not estimatable NS: MD not estimatable
Schutzman 1996 3-8 years Laceration	n=20	Fentanyl TM (n=19)	Sedation Pain	p=0.03: MD not estimatable; favours MPC NS: MD not estimatable
Bates 1994 1-4 years Laceration	n=23	Sufentanil IN + midazolam (n=19)	Pain Anxiety	NS: MD not estimatable NS: MD not estimatable
Petrack 1996 0.5-6 years Mixed	n=12	Ketamine IM; n=15	Distress Caregiver satisfaction MD satisfaction	MD –7.10 (-12.48, -1.72) favours MPC RR=1.23 (0.80, 1.89) RR=0.42 (0.21, 0.81) favours ketamine
O'Brien 1991 1.5-6 years Lacerations	n=14	Thiopental PR (n=15)	Sedation Healthcare worker satisfaction	MD=–0.30 (-1.18, 0.58) RR=0.56 (0.16, 1.92)
Terndrup 1993 <16 years Mixed	n=44	Meperidine + promethazine (n=43)	Sedation MD satisfaction	p<0.05; favours MPC; MD not estimatable NS: MD not estimatable

Table 3.9: Outcomes of benzodiazepines vs. placebo or standard care

Author/year Age range Procedure	Benzo (n)	Control (n)	Key Measures	Effect (95%CI)
Fatovich 1995 10-119 months Laceration	Midazolam PO (n=25+32)	Placebo n=23+27	Anxiety Parent distress	RR=1.42 (1.09, 1.85) favours midazolam MD=-1.60 (-2.81, -0.39) favours midazolam
Hennes 1990 0.5-6 years Laceration	Midazolam PO (n=30)	Placebo (n=25)	Anxiety	RR=5.83 (1.97, 17.30) favours midazolam
Taiwo 1992 0.5-6 years Mixed	Midazolam PO (n=16)	Placebo (n=17)	Anxiety	RR=3.54 (1.19, 10.58) favours midazolam
Shane 1994 1-4.5 years Laceration	Midazolam PR (n=16)	Placebo (n=18)	Sedation Parent anxiety	RR 11.25 (1.61, 78.46) favours midazolam MD=-4.06 (-6.75, -1.37) favours midazolam
Theroux 1993 9-59 months Laceration	Midazolam IN (n=27)	Placebo (n=17) vs. no treatment (n=15) (pooled data)	Sedation Parent satisfaction	RR 0.68 (0.47, 1.00) RR=2.05 (1.12, 3.75) favours midazolam
Luhmann 2001 2-6 years Laceration	Midazolam PO (n=51 alone vs. 52 with N_20)	Standard care (n=50 vs. 51 with N_20)	Distress Suturer satisfaction	Unclear MD=–7.00 (-18.80, -4.80) favours N_20

Table 3.10: Outcomes of benzodiazepines vs. benzodiazepines

Author/year Age range Procedure	Benzo 1 (n)	Benzo 2 (n)	Key Measures	Effect (95%CI)
Connors 1994 1-10 years Laceration	Midazolam 0.25 mg/kg IN (n = 28)	Midazolam 0.5 mg/kg PO (n = 26)	Sedation	NS: MD not estimatable
Davies 1998 1-13 years Mixed	Midazolam 0.2 mg/kg PO (n = 9)	Midazolam 0.5 mg/kg PO (n = 11; +30 after unblinding)	Pain	NS: MD not estimatable
			Anxiety scale	NS: MD not estimatable
			Parent satisfaction	High dose > low dose; RR=4 (0.80, 19.96)
Everitt 2002 1-5 years Laceration	Diazepam 0.5 mg/kg PO (n = 42)	Midazolam 1 mg/kg PO (n = 45) vs. midazolam 0.4 mg/kg IN (n = 42)	Sedation	POM=INM> POD; p<0.05; MD not estimatable
Kanegaye 2003 0.5-4 years Mixed	Midazolam 0.5 mg/kg PR (n = 32)	Midazolam 1.0 mg/kg PR (n = 33)	Sedation	High dose > low dose; p=0.004; MD not estimatable
			Parent satisfaction	NS; MD not estimatable

Table 3.11: Outcomes of benzodiazepines vs. other agents

Author/year **Age range** **Procedure**	**Benzo (n)**	**Control (n)**	**Key Measures**	**Effect (95%CI)**
Moro-Sutherland 2000 0.5-6 years CT scan	Midazolam IV (n = 26)	Pentobarbital (n = 29)	Sedation	MD=3.10 (2.62, 3.58) favours pentobarbital
Wathen 2000 0.5-16 years Mixed	Midazolam IV (n=129)	Ketamine + midazolam (n=137)	Distress MD/parent satisfaction	MD=-0.12 (-0.35, 0.11) MD RR=0.97 (0.89, 1.06); Parent RR=0.92 (0.83, 1.01)
Sherwin 2000 1-15 years Mixed	Midazolam IV (n=51)	Ketamine + midazolam IV (n=53)	No efficacy outcomes reported	
Acworth 2001 0.5-12 years Mixed	Midazolam IN (n=26)	Ketamine + midazolam IV (n=27)	Sedation Parent satisfaction MD satisfaction	MD=-2.0 (-2.89, -1.11) favours ketamine RR 1.41 (1.04, 1.91) favours Ketamine RR=0.20 (0.01, 3.97)
Younge 2000 1-7 years Laceration	Midazolam PO (n=29)	Ketamine PO (n=30)	Sedation Anxiety	p=0.039: MD not estimatable; favours ketamine NS: MD not estimatable
Havel 1999 2-18 years Orthopaedic	Midazolam IV (n=46)	Propofol IV (n=43)	Sedation	NS: MD not estimatable
Hunt 2003 >10 years Orthopaedic	Midazolam IV (n=19)	Etomidate 0.1mg/kg IV (n=20)	Sedation Success rates	MD 0.58 (-1.02, 2.18) RR=1.19 (0.98, 1.44)

Roth 2004 7.4 +/- 2.2 years (etomidate group) 8.5 +/- 1.8 years (midazolam group) Orthopaedic	Midazolam + fentanyl (n=16)	Etomidate (mean dose: 0.23 mg/kg) + fentanyl (n=21)	Distress	MD= –2.77 (-6.44, 0.90)

Table 3.12: Outcomes of benzodiazepine plus another agent vs. other agents

Author/year Age range Procedure	**Benzo + other (n)**	**Control (n)**	**Key Measures**	**Effect (95%CI)**
Hart 1997 2-8 years Mixed	Fentanyl + midazolam IV (n=13) vs. fentanyl IV (n=20)	MPC (n=9)	Sedation Pain Anxiety	NS: MD not estimatable NS: MD not estimatable NS: MD not estimatable
Kennedy 1998 5 to 15 years Orthopaedic	Ketamine + midazolam IV (n=130)	Fentanyl + midazolam IV (n=130)	Distress	MD=-1.62 (-2.04, -1.20) favours ketamine
Klein 2002 2-8 years Laceration	Fentanyl TM + midazolam PO (n=28)	Placebo + midazolam PO (n=23)	Pain Parent satisfaction	MD 0.60 (-0.97, 2.17) RR 0.85 (0.64, 1.14)
Kharasch 2000 3-13 years Orthopaedic	Fentanyl + midazolam IV (n=22)	Ketamine IV (n=21)	Pain	MD=-2.20 (-3.61, -0.79) favours fentanyl/midazolam:
Roth 2004 2-8 years Orthopaedic	Fentanyl + midazolam (n=16)	Etomidate (mean dose: 0.23 mg/kg) + fentanyl (n=21)	Distress	MD= –2.77 (-6.44, 0.90)
Luhmann 2004 4-18 years Orthopaedic	Ketamine + midazolam IV (n=55)	N_2O + hematoma block (n=47)	Distress Pain MD satisfaction	MD=-1.61 (-1.81, -1.41) favours N_2O p=0.046: MD not estimatable; favours N_2O MD=7.00 (-4.80, 18.80)

Godambe 2003 3.1-16.3 years Orthopaedic	Ketamine + midazolam IV (n=54)	Fentanyl + propofol IV (n=59)	Distress	MD=-0.20 (-0.39, -0.01) favours ketamine/midazolam
			MD/RN satisfaction	RN MD= -0.10 (-0.24, 0.04); MD MD=-0.08 (-0.21, 0.05)

Table 3.13: Outcomes of nitrous oxide (N_2O) vs. other agents

Author/year Age range Procedure	**N_2O (n)**	**Control (n)**	**Key Measures**	**Effect (95%CI)**
Gamis 1989 2-16 years Laceration	n=15	Placebo (n=19	Pain	MD=-1.60 (-4.04, 0.84) for < 8y; MD=-2.00 (-4.91, 0.91) for ≥8y
Burton 1998 2-7 years Laceration	n=17	Placebo (n=13)	Pain	MD=-5.56 (-7.54, -3.58) favours N_2O
			Anxiety	MD=-1.68 (-2.30, -1.06) favours N_2O
Luhmann 2001 2-6 years Laceration	n=51 alone vs. n=52 with midazolam PO	Standard care (n=50 vs. n=51 with midazolam PO)	Distress	Unclear
			Suturer satisfaction	MD=7.00 (-4.80, 18.80)
Luhmann 2004 (ABSTRACT) 4-18 years Orthopaedic	N_2O + hematoma block (n=47)	Ketamine + midazolam IV (n=55)	Distress	MD=-1.61 (-1.81, -1.41) favours N_2O
			Pain	p=0.046: MD not estimatable; favours N_2O
			MD satisfaction	MD=7.00 (-4.80, 18.80)

Table 3.14: Outcomes of barbiturates vs. other agents

Author/year Age range Procedure	Barbiturate (n)	Control (n)	Key Measures	Effect (95%CI)
Kienstra 2004 0.5-6 years CT scan	Pentobarbital IV (n=33)	Etomidate IV 0.3mg/kg (n=7) 0.4mg/kg (n=17); Combined n=24 Only n=17 who received 0.4mg/kg were analyzed	Success rates Motion artefact Back to baseline at discharge Parental concerns	RR=0.79 (0.06, 1.03) RR=0.21 (0.03, 1.42) RR=6.67 (2.18, 20.41) favours etomidate p=0.024; favours etomidate; RR not estimatable
Moro-Sutherland 2000 0.5-6 years CT scan	Pentobarbital IV (n = 29)	Midazolam IV (n = 26)	Sedation	MD=3.10 (2.62, 3.58) favours pentobarbital
O'Brien 1991 1.5-6 years Laceration	Thiopental PR (n=15)	MPC IM (n=14)	Sedation Healthcare worker satisfaction	MD=–0.30 (-1.18, 0.58) RR=0.56 (0.16, 1.92)

Table 3.15: Outcomes of propofol vs. other agents

Author/year **Age range** **Procedure**	**Propofol IV (n)**	**Control (n)**	**Key Measures**	**Effect (95%CI)**
Havel 1999 2-18 years Orthopaedic	Propofol IV (n=43)	Midazolam IV (n=46)	Sedation score	MD not estimatable
Godambe 2003 3-18 years Orthopaedic	Propofol + fentanyl IV (n=59)	Ketamine + midazolam (n=54)	Distress	MD=-0.20 (-0.39, -0.01) favours ketamine/midazolam
			MD/RN satisfaction	RN MD= -0.10 (-0.24, 0.04); MD MD=-0.08 (-0.21, 0.05)

Table 3.16: Outcomes of etomidate vs. other agents

Author/year Age range Procedure	**Etomidate IV (n)**	**Control (n)**	**Key Measures**	**Effect (95%CI)**
Roth 2004 7.4 +/- 2.2 years (etomidate group) 8.5 +/- 1.8 years (midazolam group) Orthopaedic	Etomidate (mean dose: 0.23 mg/kg) + fentanyl IV (n=21)	Midazolam + fentanyl IV (n=16)	Distress	MD= –2.77 (-6.44, 0.90)
Hunt 2003 >10 years Orthopaedic	Etomidate IV 0.1mg/kg (n=20)	Midazolam IV (n=19)	Sedation Success rates	MD 0.58 (-1.02, 2.18) RR=1.19 (0.98, 1.44)
Kienstra 2004 0.5-6 years CT scan	Etomidate IV 0.3mg/kg (n=7) 0.4mg/kg (n=17); Combined n=24 Only n=17 who received 0.4mg/kg were analyzed	Pentobarbital IV (n=33)	Success rates Motion artefact Back to baseline at discharge Parental concerns	RR=0.79 (0.06, 1.03) RR=0.21 (0.03, 1.42) RR=6.67 (2.18, 20.41) favours etomidate p=0.024; favours etomidate; RR not estimatable

Table 3.17: Types of times studied in randomized control trials (RCTs)

Outcome subtype	Study ID	Results	Effect (95%CI)
Time to sedation	Acworth 2001	ketamine < midazolam	p<0.001; MD not estimatable
	Bates 1994	sufentanil/midazolam < MPC	**MD=12.40 (6.99, 17.81)**
	Davies 1998	0.2mg/kg <> 0.5mg/kg	Not reported
	Everitt 2002	IN midazolam < PO diazepam	**p=0.011; MD not estimatable**
	O'Brien 1991	thiopental < MPC	p<0.01; MD not estimatable
	Petrack 1996	ketamine < MPC	p<0.001; MD not estimatable
	Younge 2001	ketamine < midazolam	p=0.001; MD not estimatable
Induction time	Kennedy 1998	fentanyl <> ketamine	MD –0.30 (-3.10, 2.50)
	Kienstra 2004	etomidate < pentobarbital	MD=2.10 (0.36, 3.84)
	Moro-Sutherland 2000	not reported	not reported
Duration of sedation	Connors 1994	IN <> PO midazolam	NS; MD not estimatable
	Godambe 2003	**propofol/fentanyl < ketamine/midazolam**	p<0.0001; MD not estimatable
	Hunt 2003	**etomidate < midazolam**	MD=19.16 (9.42, 28.90)
	Kienstra 2004	etomidate < midazolam	MD=31.30 (23.90, 38.70)
	Moro-Sutherland 2000	not reported	not reported
	Petrack 1996	ketamine <> MPC	MD=-15 (-40.46, 10.46)
	Roback 2002	IM > IV	p<0.0001; MD not estimatable
	Roth 2004	etomidate < midazolam	p<0.001; MD not estimatable

Outcome subtype	Study ID	Results	Effect (95%CI)
Time to complete procedure	Acworth 2001	Ketamine <> midazolam	MD=-2.20 (-8.96, 4.56)
	Bates 1994	sufentanil/midazolam <> MPC	MD=27.90 (11.79, 44.01)
	Kanegaye 2003	high dose <> standard dose midazolam	NS; MD not estimatable
	Kienstra 2004	etomidate < pentobarbital	MD=53.10 (41.89, 64.31)
	Klein 2002	fentanyl <> placebo	MD=-0.020 (-5.52, 5.12)
	O'Brien 1991	thiopental <> MPC	MD=4.00 (-4.91, 12.91)
	Schutzman 1994	Low dose <> High dose	NS; MD not estimatable
	Schutzman 1996	fentanyl <> MPC	MD=0.00 (-7.49,7.49)
	Shane 1994	midazolam <> placebo	MD=-2.00 (-6.71, 2.71)
	Wathen 2000	midazolam <> control	NS; MD not estimatable
Recovery time	Godambe 2003	propofol/fentanyl < ketamine/midazolam	MD=-31.40 (-41.07, -21.73)
	Havel 1999	midazolam > propofol	MD=-28.80 (-43.55, -14.05)
	Kennedy 1998	fentanyl < ketamine	MD=13.90 (2.34, 25.46)
	Kanegaye 2003	high dose <> standard dose	NS; MD not estimatable
	Luhmann 2001	midazolam > standard care	p=0.01; MD not estimatable
	Luhmann 2004	nitrous oxide < ketamine/midazolam	MD=67.50 (58.51, 76.49)
Administration until awake	Hart 1997	fentanyl < MPC	MD=-64.00 (-90.00, -37.01)
End of procedure until awake	Hart 1997	fentanyl < MPC	MD=-45.00 (-70.77, -19.23)

Outcome subtype	Study ID	Results	Effect (95%CI)
Time to discharge	Acworth 2001	ketamine > midazolam	MD=18.90 (5.24, 32.56)
	Bates 1994	sufentanil/midazolam < MPC	MD=-27.90 (-44.01, -11.79)
	Burton 1998	N2O <> O2	MD=6.50 (-1.08, 14.08)
	Davies 1998	0.2mg/kg < 0.5mg/kg	not reported
	Hunt 2003	etomidate <> midazolam	MD=2.97 (-51.56, 57.50)
	Kanegaye 2003	high dose <> standard dose	NS; MD not estimatable
	Klein 2002	fentanyl <> placebo	MD=3.00 (-8.65, 14.65)
	O'Brien 1991	thiopental < MPC	MD=31.00 (4.71, 57.29)
	Petrack 1996	ketamine < MPC	MD=-28.00 (-54.22, -1.78)
	Qureshi 1995	ketamine <> placebo	MD=14.00 (-6.07, 34.07)
	Roth 2004	etomidate < midazolam	p<0.001; MD not estimatable
	Schutzman 1994	low dose <> high dose	NS; MD not estimatable
	Schutzman 1996	fentanyl <> MPC	MD=-1.00 (-15.86, 13.86)
	Shane 1994	midazolam > placebo	MD=17.00 (9.64, 24.36)
	Sherwin 2000	midazolam <> placebo	p=0.452; MD not estimatable
	Wathen 2000	Ketamine <> midazolam	NS; MD not estimatable
	Younge 2001	ketamine <> midazolam	MD not estimatable
Time in ED	Everitt 2002	INM <> POM <> POD	NS; MD not estimatable
	Havel 1999	midazolam > propofol	MD=-23.80 (-46.67, -0.93)

Table 3.18: Adverse effects (AE) with opiates

AE/ Study	Comparison groups	Opiates n/N	Other n/N	RD [95% CI]
Desaturation (<95%; # < 90%)				
Bates 1994	MPC	1/19	1/23	0.01 [-0.12, 0.14]
Hart 1997	MPC	4/20	4/22	0.02 [-0.22, 0.26]
Kennedy 1998	ketamine	24/130	6/130	0.14 [0.06, 0.21]*
Kharasch 2000	ketamine	7/22	1/21	0.27 [0.06, 0.49]*
Klein 2002	placebo	3/28	0/23	0.11 [-0.02, 0.24]
Schutzman 1996	MPC	2/20	0/19	0.10 [-0.05, 0.25]
Godambe 2003#	ketamine	18/59	4/54	0.23 [0.09, 0.37]*
Stridor/laryngospasm				
Godambe 2003	ketamine	1/59	0/54	0.02 [-0.03, 0.06]
Kharasch 2000	ketamine	0/22	0/21	0.00 [-0.09, 0.09]
Apnoea				
Godambe 2003	ketamine	0/59	0/54	0.00 [-0.03, 0.03]
Kharasch 2000	ketamine	0/22	0/21	0.00 [-0.09, 0.09]
Dysphoric Reactions				
Godambe 2003	ketamine	0/59	3/54	-0.06 [-0.12, 0.01]
Kennedy 1998	ketamine	3/130	7/130	-0.03 [-0.08, 0.02]
Kharasch 2000	ketamine	2/22	6/21	-0.19 [-0.42, 0.03]
Vomiting				
Godambe 2003	ketamine	0/59	2/54	-0.04 [-0.10, 0.02]
Kennedy 1998	ketamine	3/130	11/130	-0.06 [-0.12, -0.01]
Klein 2002	placebo	7/26	0/21	0.27 [0.09, 0.45]*
Schutzman 1996	MPC	9/20	1/19	0.40 [0.16, 0.64]*

Table 3.19: Adverse effects (AE) with ketamine

AE/ Study	**Comparison groups**	**Ketamine n/N**	**Other n/N**	**RD [95% CI]**
Desaturation (<95%; $^{\#}$ < 90%)				
Acworth 2001	midazolam	1/26	0/26	-0.04 [-0.14, 0.06]
Kennedy 1998	fentanyl	6/130	24/130	0.14 [0.06, 0.21]*
Kharasch 2000	fentanyl + midazolam	1/21	7/22	0.27 [0.06, 0.49]*
Roback 2002	IV vs. IM	**0/41 IM**	0/39	**0.00 [-0.05, 0.05]**
Younge 2001	midazolam	**1/30**	2/29	0.04 [-0.08, 0.15]
Godambe 2003$^{\#}$	propofol	4/54	18/59	**0.23 [0.09, 0.37]***
Stridor/laryngospasm				
Godambe 2003	propofol	0/54	1/59	0.02 [-0.03, 0.06]
Kharasch 2000	fentanyl + midazolam	0/21	0/22	0.00 [-0.09, 0.09]
Qureshi 1995	placebo	0/15	0/15	0.00 [-0.12, 0.12]
Apnoea				
Godambe 2003	propofol	0/54	0/59	0.00 [-0.03, 0.03]
Kharasch 2000	fentanyl + midazolam	0/21	0/22	0.00 [-0.09, 0.09]
Dysphoric Reactions				
Acworth 2001	midazolam			
Godambe 2003	propofol	3/54	0/59	-0.06 [-0.12, 0.01]
Kennedy 1998	fentanyl	7/130	3/130	-0.03 [-0.08, 0.02]
Kharasch 2000	fentanyl + midazolam	6/21	2/22	-0.19 [-0.42, 0.03]
Qureshi 1995	placebo	0/15	0/15	0.00 [-0.12, 0.12]
Younge 2001	midazolam	0/30	6/29	0.21 [0.05, 0.36]*
Vomiting				
Acworth 2001	midazolam	2/26	1/26	-0.04 [-0.16, 0.09]
Godambe 2003	propofol	2/54	0/59	-0.04 [-0.10, 0.02]
Kennedy 1998	fentanyl	11/130	3/130	-0.06 [-0.12, -0.01]
Qureshi 1995	placebo	2/15	0/15	-0.13 [-0.33, 0.06]
Roback 2002	IV vs. IM	0/41 IM	0/39	0.00 [-0.05, 0.05]
Younge 2001	midazolam	2/30	6/29	0.14 [-0.03, 0.31]

Table 3.20: Adverse effects (AE) with benzodiazepines

AE/ Study	Comparison groups	Benzo n/N	Other n/N	RD [95% CI]
Desaturation (<95%; # < 90%)				
Godambe 2003	**propofol**	10/24	2/24	0.33 [0.11, 0.56]*
Hart 1997	fentanyl; MPC	3/13	5/29	0.06 [-0.21, 0.33]
Havel 1999	propofol	5/46	**5/43**	-0.01 [-0.14, 0.12]
Kharasch 2000	ketamine	7/22	1/21	0.27 [0.06, 0.49]*
Luhmann 2004	N_2O	4/55	0/47	0.07 [0.00, 0.15]
Moro-Sutherland 2000	pentobarbital	0/26	4/29	-0.14 [-0.28, 0.00]
Sherwin 2000	**placebo**	2/53	1/51	0.02 [-0.05, 0.08]
Younge 2001	ketamine	2/29	1/30	0.04 [-0.08, 0.15]
Godambe 2003#	propofol	4/54	18/59	-0.23 [-0.37, -0.09]
Wathen 2000#	placebo	9/129	2/137	0.06 [0.01, 0.10]*
Stridor/laryngospasm				
Godambe 2003	propofol	0/54	1/59	-0.02 [-0.06, 0.03]
Kharasch 2000	ketamine	0/22	0/21	0.00 [-0.09, 0.09]
Wathen 2000	placebo	2/129	0/137	0.02 [-0.01, 0.04]
Apnoea				
Godambe 2003	propofol	0/54	0/59	0.00 [-0.03, 0.03]
Kharasch 2000	ketamine	0/22	0/21	0.00 [-0.09, 0.09]
Wathen 2000	placebo	1/129	1/137	0.00 [-0.02, 0.02]
Vomiting				
Godambe 2003	propofol	2/54	0/59	0.04 [-0.02, 0.10]
Luhmann 2001	N_2O	0/51	5/51	-0.10 [-0.19, -0.01]
Sherwin 2000	placebo	1/53	6/51	-0.10 [-0.19, 0.00]
Wathen 2000	placebo	12/129	27/137	-0.10 [-0.19, -0.02]
Younge 2001	ketamine	6/29	2/30	0.14 [-0.03, 0.31]
Dysphoric Reactions				
Godambe 2003	propofol	3/54	0/59	0.06 [-0.01, 0.12]
Havel 1999	propofol	3/46	2/43	0.02 [-0.08, 0.11]
Kharasch 2000	ketamine	2/22	6/21	-0.19 [-0.42, 0.03]
Wathen 2000	placebo	8/129	10/137	-0.01 [-0.07, 0.05]
Younge 2001	ketamine	6/29	0/30	0.21 [0.05, 0.36]*

Table 3.21: Adverse effects (AE) with N_2O

AE/ Study	Comparison groups	N_2O n/N	Other n/N	RD [95% CI]
Vomiting				
Burton 1998	oxygen	1/17	0/13	0.06 [-0.10, 0.22]
Gamis 1989	oxygen	1/15	0/19	0.07 [-0.09, 0.23]
Luhmann 2001	midazolam	5/51	0/51	0.10 [0.01, 0.19]*

Table 3.22: Adverse effects (AE) with barbiturates

AE/ Study	Comparison groups	Barbiturate n/N	Other n/N	RD [95% CI]
Desaturation (<95%)				
Moro-Sutherland 2000	midazolam	4/29	0/26	0.14 [0.00, 0.28]
O'Brien 1991	MPC	0/15	0/14	0.00 [-0.12, 0.12]

Table 3.23: Adverse effects (AE) with propofol

AE/ Study	Comparison groups	Propofol n/N	Other n/N	RD [95% CI]
Desaturation (<95%; # < 90%)				
Godambe 2003	ketamine	10/24	2/24	0.33 [0.11, 0.56]*
Havel 1999	midazolam	5/43	5/46	0.01 [-0.12, 0.14]
Godambe 2003#	ketamine	18/59	4/54	0.23 [0.09, 0.37]*
Stridor/laryngospasm				
Godambe 2003	ketamine	1/59	0/54	0.02 [-0.03, 0.06]
Apnoea				
Godambe 2003	ketamine	0/59	0/54	0.00 [-0.03, 0.03]
Dysphoric Reactions				
Godambe 2003	ketamine	0/59	3/54	-0.06 [-0.12, 0.01]
Havel 1999	midazolam	2/43	3/46	-0.02 [-0.11, 0.08]

Table 3.24: Adverse effects (AE) with etomidate

AE/ Study	Comparison groups	Etomidate n/N	Other n/N	RD [95% CI]
Desaturation (<95%)				
Roth 2004	Midazolam +fentanyl	0/26	0/16	0.00 [-0.10, 0.10]
Airway obstruction				
Roth 2004	Midazolam +fentanyl	0/21	5/16	-0.31 [-0.54, -0.08]*
Apnoea				
Roth 2004	Midazolam +fentanyl	0/21	0/16	0.00 [-0.10, 0.10]
Vomiting				
Roth 2004	Midazolam +fentanyl	0/21	0/16	0.00 [-0.10, 0.10]

Figures

Figure 3.1: Metaview of benzodiazepines vs. other sedatives

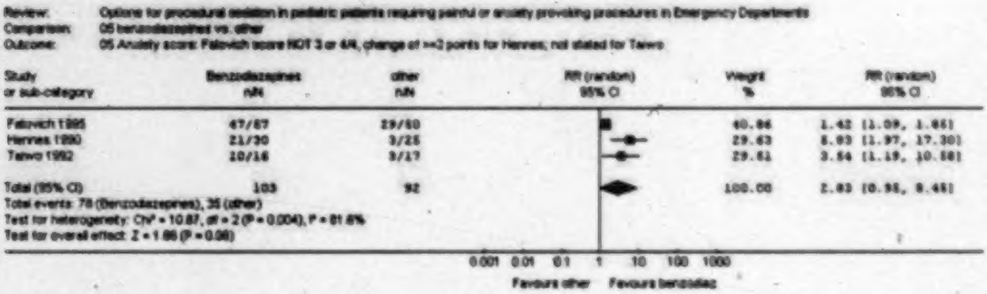


Figure 3.2: Metaview of nitrous oxide (N_2O) vs. other sedatives

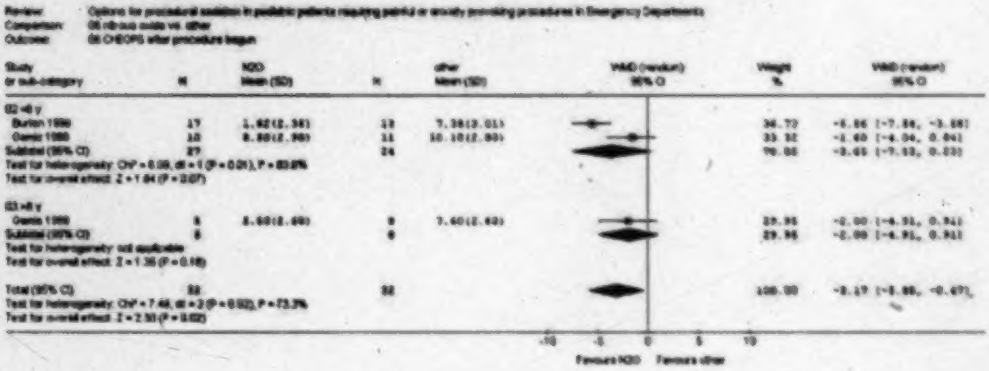


Figure 3.3: Graph of times to discharge by different sedatives

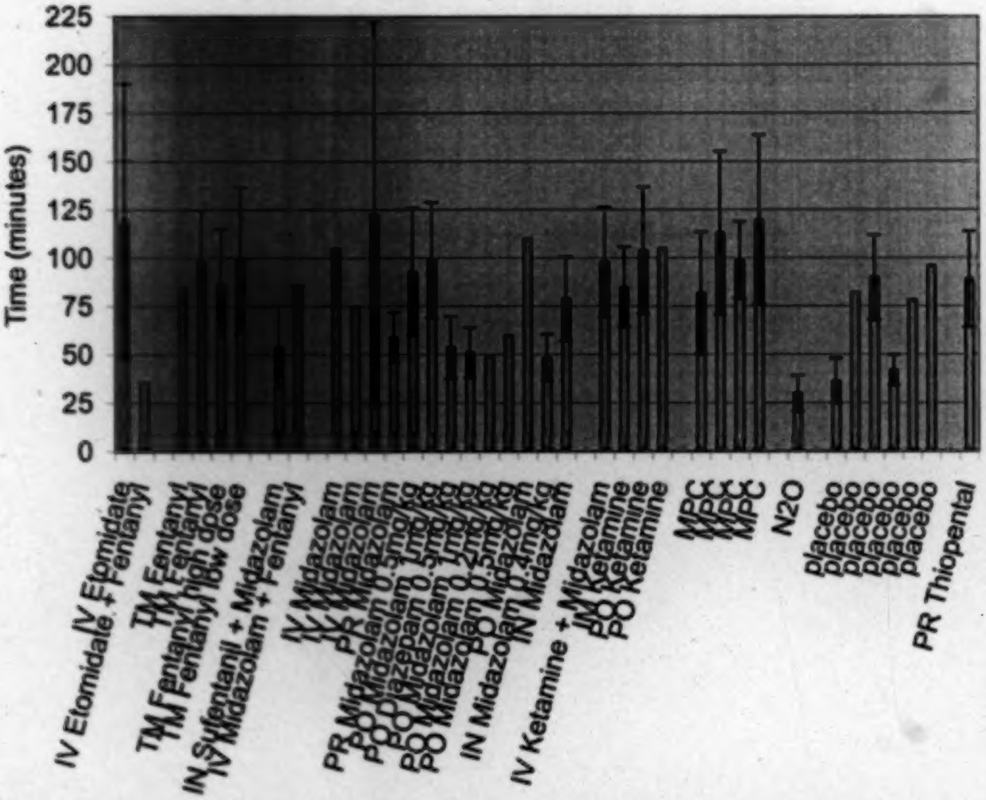
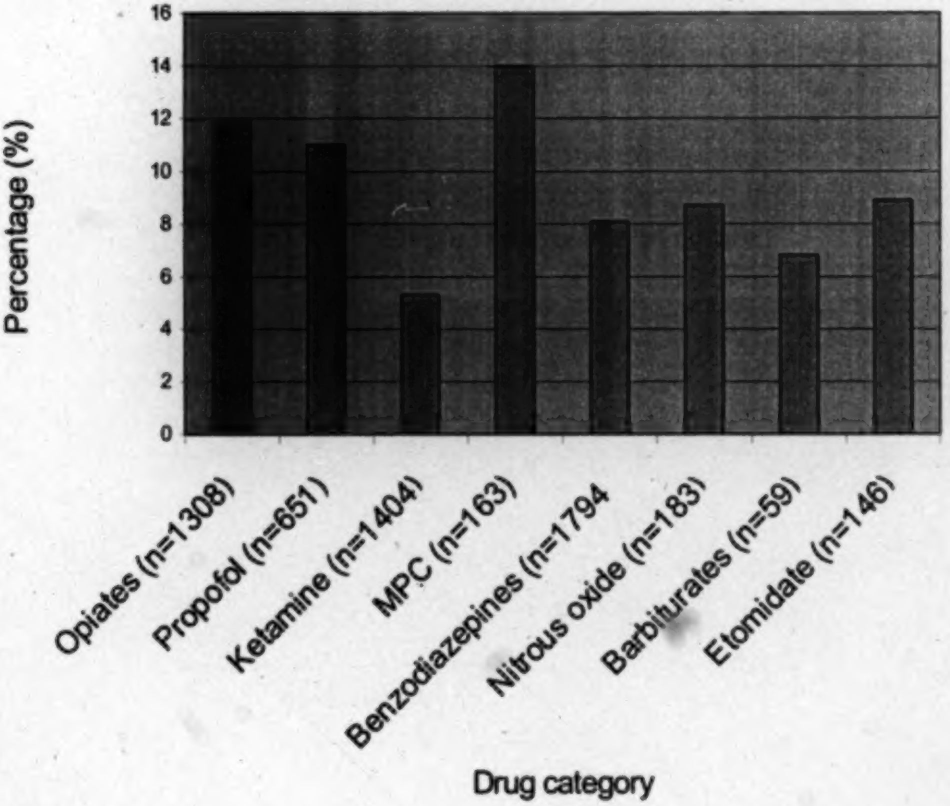


Figure 3.3: Graph of times to discharge by different sedatives. Times from medications of individual study groups from each RCT were reported separately.

Figure 3.4: Percentage (%) of adverse effects that occurred



Reference List for Chapter 3

(1) Acworth JP, Purdie D, Clark RC. Intravenous ketamine plus midazolam is superior to intranasal midazolam for emergency paediatric procedural sedation. Emergency Medicine Journal 2001; 18:39-45.

(2) American Academy of Pediatrics Committee on Drugs. Reappraisal of lytic cocktail/demerol, phenergan, and thorazine (DPT) for the sedation of children. American Academy of Pediatrics Committee on Drugs. Pediatrics 1995; 95:598-602.

(3) Bates BA, Schutzman SA, Fleisher GR. A comparison of intranasal sufentanil and midazolam to intramuscular meperidine, promethazine, and chlorpromazine for conscious sedation in children. Annals of Emergency Medicine 1994; 24:646-51.

(4) Burton JH, Auble TE, Fuchs SM. Effectiveness of 50% nitrous oxide/50% oxygen during laceration repair in children. Academic Emergency Medicine 1998; 5:112-7.

(5) Connors K, Terndrup TE. Nasal versus oral midazolam for sedation of anxious children undergoing laceration repair. Annals of Emergency Medicine 1994; 24:1074-9.

(6) Davies FC, Waters M. Oral midazolam for conscious sedation of children during minor procedures. Journal of Accident & Emergency Medicine 1998; 15:244-8.

(7) Evered L, Klassen TP, Hartling L, Wiebe N, Rowe BH. Options for procedural sedation in pediatric patients requiring painful or anxiety provoking procedures in Emergency Departments (Protocol). The Cochrane Library, Issue 1, 2005. Chichester, UK: John Wiley & Sons, Ltd.

(8) Everitt IJ, Barnett P. Comparison of two benzodiazepines used for sedation of children undergoing suturing of a laceration in an emergency department. Pediatric Emergency Care 2002; 18:72-4.

(9) Fatovich DM, Jacobs IG. A randomized, controlled trial of oral midazolam and buffered lidocaine for suturing lacerations in children (the SLIC Trial). Annals of Emergency Medicine 1995; 25:209-14.

(10) Gamis AS, Knapp JF, Glenski JA. Nitrous oxide analgesia in a pediatric emergency department. Annals of Emergency Medicine 1989; 18:177-81.

(11) Godambe SA, Elliot V, Matheny D, Pershad J. Comparison of propofol/fentanyl versus ketamine/midazolam for brief orthopedic procedural sedation in a pediatric emergency department. Pediatrics 2003; 112:116-23.

(12) Hart LS, Berns SD, Houck CS, Boenning DA. The value of end-tidal CO_2 monitoring when comparing three methods of conscious sedation for

children undergoing painful procedures in the emergency department. Pediatric Emergency Care 1997; 13:189-93.

(13) Havel CJ, Jr., Strait RT, Hennes H. A clinical trial of propofol vs midazolam for procedural sedation in a pediatric emergency department. Academic Emergency Medicine 1999; 6:989-97.

(14) Hennes HM, Wagner V, Bonadio WA, Glaeser PW, Losek JD, Walsh-Kelly CM et al. The effect of oral midazolam on anxiety of preschool children during laceration repair. Annals of Emergency Medicine 1990; 9:1006-1009.

(15) Hunt GS, Spencer MT. Etomidate and midazolam for procedural sedation: prospective trial. Annals of Emergency Medicine 2003; 42: 540.

(16) Ioannidis JP, Lau J. Completeness of safety reporting in randomized trials: an evaluation of 7 medical areas. JAMA 2001; 285(4):437-43.

(17) Kanegaye JT, Favela JL, Acosta M, Bank DE. High-dose rectal midazolam for pediatric procedures: a randomized trial of sedative efficacy and agitation. Pediatric Emergency Care 2003; 5:329-336.

(18) Kennedy RM, Porter FL, Miller JP, Jaffe DM. Comparison of fentanyl/midazolam with ketamine/midazolam for pediatric orthopedic emergencies. Pediatrics 1998; 102:956-63.

(19) Kharasch SJ, Chand R, Kastner B, Bauchner H. Is ketamine the sedative of choice for closed fracture reduction in children? A randomized trial of ketamine versus fentanyl/midazolam (Abstract). Pediatric Academic Society/Society of Pediatric Research Annual Meeting, May 2003.

(20) Kienstra AJ, Ward MA, Sasan F, Hunter JV, Morriss MC, Macias CG. Etomidate vs. pentobarbital for sedation of children for head and neck CT imaging (Abstract). Pediatric Academic Society/Society of Pediatric Research Annual Meeting, May 2003..

(21) Klein EJ, Diekema DS, Paris CA, Quan L, Cohen M, Seidel KD. A randomized, clinical trial of oral midazolam plus placebo versus oral midazolam plus oral transmucosal fentanyl for sedation during laceration repair. Pediatrics 2002; 109:894-7.

(22) Luhmann JD, Kennedy RM, Porter FL, Miller JP, Jaffe DM. A randomized clinical trial of continuous-flow nitrous oxide and midazolam for sedation of young children during laceration repair. Annals of Emergency Medicine 2001; 37:20-7.

(23) Luhmann JD, Schootman M, Voytas L, Luhmann SJ, Kennedy RM. A comparison of ketamine/midazolam and nitrous oxide/hematoma block for forearm fracture reduction in children (Abstract). Pediatric Academic Societies' Annual Meeting, May 2004.

(24) Moro-Sutherland DM, Algren JT, Louis PT, Kozinetz CA, Shook JE. Comparison of intravenous midazolam with pentobarbital for sedation for

head computed tomography imaging. Academic Emergency Medicine 2000; 7:1370-5.

(25) O'Brien JF, Falk JL, Carey BE, Malone LC. Rectal thiopental compared with intramuscular meperidine, promethazine, and chlorpromazine for pediatric sedation. Annals of Emergency Medicine 1991; 20:644-647.

(26) Petrack EM, Marx CM, Wright MS. Intramuscular ketamine is superior to meperidine, promethazine, and chlorpromazine for pediatric emergency department sedation]. Archives of Pediatrics & Adolescent Medicine 1996; 150:676-81.

(27) Qureshi FA, Mellis PT, McFadden MA. Efficacy of oral ketamine for providing sedation and analgesia to children requiring laceration repair. Pediatric Emergency Care 1995; 11:93-7.

(28) Roback MG, Wathen JD, Mackenzie T, Hurley D. Length of sedation with ketamine administered IV vs. IM in a PED. Annals of Emergency Medicine 2004; 11:488-489.

(29) Roth KR, Herr SM, Pitetti RD, Zucherbraun NS, Fine GF, King C. Comparison of etomidate and fentanyl with midazolam and fentanyl for sedation and analgesia during fracture in a pediatric ED (Abstract).Pediatric Academic Society/Society of Pediatric Research Annual Meeting, May 2004.

(30) Schutzman SA, Burg J, Liebelt E, Strafford M, Schechter N, Wisk M et al. Oral transmucosal fentanyl citrate for premedication of children undergoing laceration repair. Annals of Emergency Medicine 1994; 24:1059-64.

(31) Schutzman SA, Liebelt E, Wisk M, Burg J. Comparison of oral transmucosal fentanyl citrate and intramuscular meperidine, promethazine, and chlorpromazine for conscious sedation of children undergoing laceration repair. Annals of Emergency Medicine 1996; 28:385-90.

(32) Shane SA, Fuchs SM, Khine H. Efficacy of rectal midazolam for the sedation of preschool children undergoing laceration repair. Annals of Emergency Medicine 1994; 24:1065-73.

(33) Sherwin TS, Green SM, Khan A, Chapman DS, Dannenberg B. Does adjunctive midazolam reduce recovery agitation after ketamine sedation for pediatric procedures? A randomized, double-blind, placebo-controlled trial. Annals of Emergency Medicine 2000; 35:229-38.

(34) Singer A, Richman P Kowalska A et al. Comparison of patient and practitioner assessments of pain from commonly performed emergency department procedures. Annals of Emergency Medicine 1999; 33:652-658.

(35) Taiwo B, Flowers M, Zoltie N. Reducing children's fear when undergoing painful procedures. Archives of Emergency Medicine 1992; 9:306-9.

(36) Terndrup TE, Dire DJ, Madden CM, Gavula D, Cantor RM. Comparison of intramuscular meperidine and promethazine with and without chlorpromazine: a randomized, prospective, double-blind trial. Annals of Emergency Medicine 1993; 22:206-11.

(37) Theroux MC, West DW, Corddry DH, Hyde PM, Bachrach SJ, Cronan KM et al. Efficacy of intranasal midazolam in facilitating suturing of lacerations in preschool children in the emergency department. Pediatrics 1993; 91:624-7.

(38) Wathen JE, Roback MG, Mackenzie T, Bothner JP. Does midazolam alter the clinical effects of intravenous ketamine sedation in children? A double-blind, randomized, controlled, emergency department trial. Annals of Emergency Medicine 2000; 36:579-88.

(39) Younge PA, Kendall JM. Sedation for children requiring wound repair: a randomized controlled double blind comparison of oral midazolam and oral ketamine. Emergency Medicine Journal 2001; 18:30-3.

(40) Merck & Co.,Inc. Merck Announces Voluntary Worldwide Withdrawal of VIOXX®. 2004. Accessed on 30 January 2005 at: http://www.vioxx.com/rofecoxib/vioxx/consumer/index.jsp

Chapter Four: Future directions

Section 4.1: Introduction to future directions

In the previous three chapters I have discussed the need for procedural sedation in Paediatric emergency medicine; evaluated the quality of the research conducted in this field; and, examined the evidence for and against the use of a variety of agents in this setting. No universal agent exists which is safe for all ages, effective for all procedures, relatively inexpensive and available for procedural sedation in the emergency department (ED). The current selection of an agent for sedation of children undergoing painful or anxiety-provoking procedures in the ED depends on the procedure, its duration, and the characteristics of the child.

Overall, the findings from this systematic review of procedural sedatives indicate that more research is needed. Most importantly, this is a field that is evolving and clinicians and patients deserve better quality evidence upon which to base their decisions than currently exists. There are a number of steps that are required to advance this field including a survey of current practice, a chart review of current practices, and randomized controlled trials involving paediatric patients to better evaluate the agents that are currently in use. Further advances would include creation of Clinical Practice Guidelines (CPGs) to summarise any recommendations for use by clinicians. The following sections will outline the potential next steps that stem from the findings of this systematic review.

Section 4.2: Survey

Practice varies for procedural sedation from physician to physician. It would be extremely useful to know more about the current practice for procedural sedation across Canada, and a national survey of emergency physicians would be helpful to define the current standard of care. Questions that need to be answered include:

1. For which procedures are emergency physicians commonly performing sedation in the paediatric population (ages 1 month - 17 years)?
2. What medications are being used for the purpose of paediatric procedural sedation?
3. On what basis are physicians choosing one sedative over another for procedural sedation of children in the ED?
4. What protocols (if any; and based on what evidence) are being followed for:
    a. Pre-sedation assessment including fasting times
    b. Sedation protocols
    c. Discharge criteria

5. What personnel are being utilized (how many doctors of which training background and from what level of training, nurses, respiratory therapists, other)?

An electronic and/or paper-based survey would be the best method of obtaining this information. Paper-based surveys are readily accepted and understood by most physicians. There are inherent problems with paper-based surveys, including low response rates, long response times, illegible and incomplete data, data entry errors and expense.(5) Electronic surveys, conducted via email and/or over the Internet, attempt to deal with many of these problems. One theoretical risk of collecting data using these electronic formats is that tampering may occur. Other problems with web-based surveys do not apply when used in this setting, including inaccessibility due to lack of Internet access or illiteracy. Research on surveys of different formats has failed to demonstrate clear advantage of one method over the other.(6) Important factors to consider when creating such a survey include:

1. The purpose would be to describe the sedating practices of Canadian emergency physicians and departments that care for children.
2. Clearly define the study population. It would be useful to obtain information from physicians who practice paediatric emergency medicine, as well as physicians across Canada who work in *general* EDs (serving both adults and children). Surveying the clinicians in general EDs that see all ages would provide different information that would be interesting to compare. Lastly, including rural EDs would add yet another dimension to the information obtained, as there are different challenges to be dealt with outside of the busy urban ED environment.
3. A survey of Medical Site Chiefs for Paediatric, General and Rural EDs would also provide information regarding the institutional requirements for procedural sedation, including a presence of a procedural sedation form, specific paediatric form, audit procedures (if any), complications, concerns raised, etc.
4. An appropriate sampling method would have to be used, to maximize the response rate. Surveyed doctors are less likely to respond to surveys that are excessively long and/or labour intensive. Canadian Association of Emergency Physicians (CAEP) and the Paediatric Emergency Research of Canada (PERC) group members clearly need to be surveyed, as these bodies represent physicians most likely to perform procedural sedation. Sites to sample from should be as inclusive as possible, so that all relevant range of departments would be sampled. The method would also need to be easily accessible and facilitate a good response rate. The sample should strive to include all paediatric emergency physicians across the country.

The goal of this survey would be to gain insight into the practice variation across Canada for procedural sedation. The information acquired could be used to determine what research questions are most needed, and what information a CPG could provide to improve care across the country.

Section 4.3: The Chart Review

In addition to exploring current practice across the country, it would be useful to document specific practice variation within one institution by performing a structured chart review. Charts to be included would be those of paediatric patients who had undergone sedation with or without analgesia for painful or anxiety provoking procedures in the paediatric ED at the Stollery Children's Hospital within the last two years. This would provide a reasonable sample of files within a time frame that would be relevant. There are approximately 1800 sedations performed annually, and charts may be identified by hospital codes.

Important information would be collected primarily from standard procedural sedation and ED records using a standardized data collection form. Data to record would include patient demographics (age, gender), which procedures were performed (e.g., laceration repair, reduction of dislocation, reduction of fracture, cardioversion, etc), drugs (agents, dose {mg or mcg/kg} and route) administered for the purpose of sedation as well as adjunctive medications, personnel involved (number and professional affiliation), monitoring performed and vital signs taken, level of consciousness, recorded times (such as to sedation, duration of sedation, and time in the ED) and adverse events. Adverse effects would be classified as either present or absent, and include apnoea (> 30 seconds), desaturation (< 95% oxygen saturation by pulse oximetry with or without oxygen supplementation), bag valve mask ventilation or intubation, emesis, aspiration, hypotension, myoclonus, inadequate sedation, unsuccessful procedure, pruritis, pain on injection, agitation, emergency phenomena and cardiac arrest. The remainder of the medical records would be reviewed to ascertain whether any adverse events led to significant morbidity or mortality.

The ultimate use of this chart review would be to gain insight into the practice variation for procedural sedation within one department. The information acquired could be used to determine what research questions should next be addressed, as well as to establish what information a CPG could provide to improve care within one department.

Section 4.4: Randomized controlled trials

Information collected through the survey of current practice and chart review could be used to develop a randomized controlled trial to evaluate treatment options regarding procedural sedation with the ultimate goal of identifying the optimal therapeutic approach. The following are some considerations for the design of a trial with high internal and external validity.

4.4.1 Population

The study population should include children with the following characteristics:

1. Age: The minimum should be at least one month, to eliminate neonates; the maximum should be 18 years old. While this age range is broad, there is no reason to suspect that children (beyond the neonatal period) of different ages should respond differently to sedating agents. Previous RCTs have studied children down to 2 years of age.(28;29) This makes it challenging for the clinician to extrapolate the conclusions to younger infants, who often require sedation.

2. Setting: Patients must be those presenting to an ED. There is clearly a different set of characteristics in a patient presenting to the ED than those booked for elective surgery in an operating room or outpatient procedures in the dental office. Section 1.1.5 outlined unique aspects of subjects that present to the ED setting, including the variety of diagnoses and levels of acuity. Injuries are acute and unexpected, and patients may have concurrent or co-morbid illness, and full stomachs.

3. Procedures: Subjects must require painful and/or anxiety-provoking procedures that have been defined *a priori*. Potential procedures that meet these requirements are described in Section 1.1.4. It would be most useful to restrict the study to laceration repair, reduction of dislocations, and reduction of fractures, as these are the most common procedures performed and would permit generalizability to most ED patients.

4.4.2 Intervention

The survey would help guide the choice of agents for comparison. Subjects in the study group of the ideal RCT must be administered some form of sedation, while those in the control group are given another form of sedation (e.g. different medication, dose and/or route). Based on review of the literature in this thesis, a potentially useful comparison would be propofol or etomidate plus fentanyl versus ketamine. These drugs sedate with similar efficacy without providing analgesia, they work in a similar time frame, and are both used for the purposes of procedural sedation. Etomidate is not yet available in Canada for use in this role in children, but it has been used in the United States. The reason etomidate should be considered is that it has been associated with less cardio-respiratory adverse effects, and is theoretically an equally effective sedative.

4.4.3 Outcome measures

The use of appropriate, valid, well-defined, relevant outcome measures is critical. Standardization in the outcome measures used would facilitate comparisons across studies as well as pooling of the results in a meta-analysis.

1. The most obvious outcome measure of interest in a study evaluating a sedative is the efficacy of that sedative. There are many ways to measure such efficacy, directly and indirectly. When selecting a scale to evaluate patient sedation, it is critical to ensure that it is truly measuring what it purports to measure. The scale should also be designed and validated for use in similar populations. For example, the Ramsay Sedation score (Appendix 3.3) has been used in many studies in this systematic review, and has been validated. (1;11;13;16;17) The Children's Hospital of Wisconsin Sedation Scale for procedural sedation in children (Table 4.1) is recommended by the American Academy of Pediatrics as well as the American Society of Anesthesiologists for use in this population.(12) It is based on the Ramsay scale. This scale should be studied for validity before it is promoted for use in an RCT.

2. Another outcome to be measured is time. In general, times are practically relevant and defined clearly, so that replication and potential comparisons are feasible. Two types of times should be observed: 1) practical and clinically applicable times (e.g. total time in the department), that clinicians will seek to decide if that medication increased ED times; and, 2) times that reflect the pharmacology of the drug and will provide a clear indication of the time to onset as well as the duration of action. These latter times are not confounded by factors unrelated to the drug itself, such as mandatory observation periods following procedural sedation and ED volumes and pressures.

3. RCTs may not be the most appropriate design with which to formally assess adverse effects.(3) Clinically significant effects (e.g. respiratory depression, cardiovascular depression) are rare, and require very large studies to evaluate. It is, however, critical to include documentation of any potential adverse effects that are known to occur with a study drug, whether or not they occur. It is important to conduct appropriate studies of adverse effects in the future.

4. A final outcome measure that should be recorded is the financial cost. Expenses to note would include medications and equipment used (such as single use oxygen masks, oxygen saturation probes, etc), salaries for all professionals involved (if the alternative to procedural sedation would

be for the patient to be taken to the operating room), and expenses incurred by the families, such as lost work time if the patient was required to stay overnight or longer awaiting an operating room time.

4.4.4 Design

The design of the ideal RCT would include several critical factors. The randomization should be performed using an accepted method (e.g., computer-generated technique). Ensuring multiple levels of blinding, including the individual, the health care team, the data collectors, the investigators, the analyst as well as the data safety monitoring board, would also minimize bias. A well-designed RCT would ensure concealment of allocation, so as to prevent the possibility that the researchers (unconsciously or otherwise) can influence which patients are assigned to a given intervention group. One other important aspect of designing this RCT includes management of dropouts and withdrawals. These must be included in the final analysis, following an intention-to-treat protocol. In addition, the reasons for withdrawal from the study should be detailed.

4.4.5 Advantages and disadvantages of a multi-centre trial

One of the challenges of doing any clinical research is how to best achieve an adequate sample size. Evaluating the efficacy of etomidate versus propofol using the Children's Hospital of Wisconsin Sedation Scale as the primary outcome may require a larger sample size than is practically feasible at one site within a reasonable time frame. Performing a multi-centre trial, involving EDs across Canada, may solve such a problem. The benefit of this approach would be that it would permit recruitment of a large sample size in a more timely fashion.

There are limitations to multi-centre trials, however, that must be weighed against this benefit. These include difficulty in following a common protocol due to variation in institutional mandatory guidelines for sedation, differences in availability of study drugs, and the challenges of conducting research over large physical distances. If it becomes clear that the benefits of a multi-centre trial outweigh the drawbacks, the centres to be involved must be chosen. The question then becomes: is it a study that is best performed in paediatric EDs, or would there be advantages to including general emergency departments?

In paediatrics, the decision surrounding multi-centred research is made easier by the existence of a group called the "Paediatric Emergency Research Canada" (PERC). PERC is a network of health care professionals with an interest in paediatric emergency medicine. It was formed in 1995 and currently ten out of the eleven Canadian children's emergency departments are actively involved in PERC studies. It is logical that a study involving paediatric emergency patients would be ideal for such a collaboration. The only drawback to restricting the study to paediatric EDs would be the potential criticism of being unable to extrapolate these findings to a general ED. It is not known if this criticism is valid, and there is no practical reason that a protocol studied in a paediatric ED could not be used in a general ED.

4.4.6 Funding

The budget for a multi-centre RCT that involves medications and video equipment will be expensive. Funding will be required, and potentially sought from the Canadian Institutes of Health Research (CIHR), as well as the local funding agencies such as the Alberta Heritage Foundation for Medical Research (AHFMR).

An example budget will need to include the following:

a. Medications (propofol, etomidate, lidocaine, fentanyl, naloxone)
b. Pharmacy costs for randomization/medication preparation
c. Personnel (research assistants to collect and enter data, statistician)
d. Equipment:
    1. Video camera
    2. Videotapes
    3. Aluminium foil for intravenous tubing
e. Communication: Pagers
f. Travel

Section 4.5: Clinical Practice Guidelines

4.5.1 Rationale

Physicians often face complex and difficult decisions, and may not be aware of the most up-to-date evidence on which to base their choices. Clinical Practice Guidelines (CPGs) have been defined as "systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances".(8)

One reason for the development of CPGs is to attempt to standardize treatment, with the aim of turning away from the imposition of guidelines by constituencies that have less clinical scientific goals (cost containment, bureaucratic simplicity, spreading potentially idiosyncratic personal opinion). It needs to be highlighted that guidelines are never a substitute for good clinical judgment and common sense.

CPGs suggest value judgments about the relative significance of various health and economic outcomes, and are intended to influence practitioner's decisions. CPGs help by providing evidence-based recommendations for daily use in a particular clinical setting. Ideally, they are prepared by systematically gathering, and evaluating evidence regarding the various options for a particular clinical scenario, and provide a practical recommendation for care. The strength of the evidence for each recommendation also should be indicated.

Once created, the draft CPG may then be sent for peer review to experts in the field, and may be pilot tested to ensure its applicability. It should indicate when it would be reviewed and updated as needed. Guidelines for preparation of CPGs have been created by the Canadian Medical Association(7) and are detailed on their website as well as in articles published in 1995.(2;4;14) The process for creating CPGs is outlined in the Figure 4.1.

4.5.2 Consensus development

Designing a CPG may be done in conjunction with many of the leading experts in the field. The available research in the area of procedural sedation does not, and cannot possibly, address all the variations and contingencies that arise in clinical practice. Most research is difficult to generalize to everyday clinical practice, and this is particularly so for paediatric procedural sedation. CPGs help with those patients who do not meet the narrow selection criteria used in most research studies. Expert-generated guidelines could be helpful because clinical practice is so complicated that it is constantly generating far too many questions for the clinical research literature to ever answer comprehensively with systematic studies.

Another reason for considering CPGs developed using consensus of experts is that the rate of changes in the accepted best clinical practice often is much faster than research that confirms or refutes the choices.

4.5.3 Monitoring forms

The following information would be useful in monitoring the CPG(15):

a. Validity of the guideline: Use of guideline leads to improvements in sedation score and patient comfort.
b. Reliability: Given the same clinical circumstances another health professional applies them similarly.
c. Reproducibility: Given the same evidence another guideline group produces similar recommendations.
d. Clinical applicability: The defined target population is in accordance with scientific evidence.
e. Clinical flexibility: Exceptions are identified and incorporated in decision-making.
f. Cost effectiveness: Use of the guidelines leads to improvements in health at acceptable costs.
g. Clarity: Definitions are precise, user-friendly and use unambiguous language.

h. Multidisciplinary Process: All key disciplines and interests (including patients) contribute to guideline development.
i. Documentation: Participants, assumptions, and methods are recorded; and recommendations are linked to available evidence.
j. Scheduled Review: The guidelines state when and how they are to be reviewed.

4.5.4 Outcome studies

Following the implementation of a CPG, it would be important to evaluate the compliance and outcomes following its implementation. A "before and after" study could be performed to determine if the CPG had an impact on clinical management of patients. The study would be most useful if it was designed prior to implementation of the CPG, so that the outcome measures (such as The Children's Hospital of Wisconsin Sedation Scale(12)) could be consistently measured.

Section 4.6: Summary

The sedation of children who undergo painful or anxiety provoking procedures is a common and important area of patient care. While maximizing the comfort of the child is the primary goal, it is critical that staff and resources are used in a cost-effective manner. Previous research to find the ideal agent, dose and route of delivery for procedural sedation in children is weak and does not clarify care; consequently, much work remains. A great deal of research is required in this area in the future, including surveying the current practices, performing a local chart review to understand details of what complications have arisen, conducting a randomized controlled trial to compare the two agents that appear to be as close to ideal as possible, and developing clinical practice guidelines.

Table

Table 4.1 Children's Hospital of Wisconsin Sedation Scale (17)

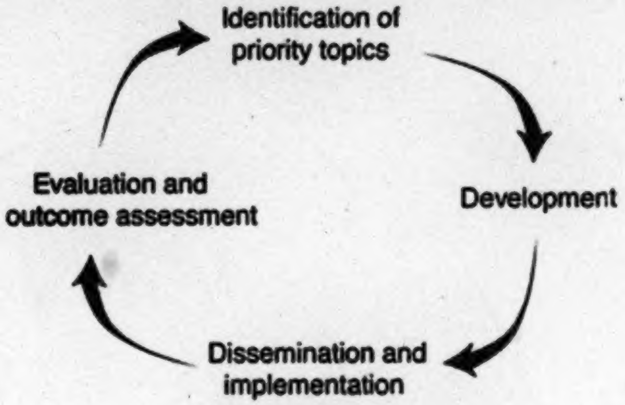
Level of Consciousness	**Stimulus**	**Score**
Agitated anxious in pain	Spontaneous without stimulus	6
Awake and calm	Spontaneous without stimulus	5
Drowsy with eyes open or closed, easily aroused	With mild to moderate verbal stimulus	4
Drowsy, arousable	Moderate tactile or loud verbal	3
Can be aroused to consciousness but slow	Requires sustained painful stimulus	2
Can be aroused but not to consciousness	Requires sustained painful stimulus	1
Unresponsive	No response to painful stimuli	0

Score	**Interpretation**
6	Inadequate sedation
5	Minimal conscious sedation
4	Conscious sedation moderate
3	Conscious sedation moderate to deep
2	Conscious sedation deep
1	<Excessive sedation>
0	Anaesthesia

Scores of 4-5 are classified as having received conscious sedation and <=3 as having received deep sedation.

Figure

Figure 4.1: Process for creating Clinical Practice Guidelines


Identification of priority topics
Development
Dissemination and implementation
Evaluation and outcome assessment

(adapted from (7))

Reference List for Chapter 4

(1) Avramov MN, White PF. Methods for monitoring the level of sedation. Critical Care Clinics 1995; 11:803-26.

(2) Basinski AS. Evaluation of clinical practice guidelines. Canadian Medical Association Journal 1995; 153:1575-81.

(3) Bastian H, Middleton P. More good than harm: How well can Cochrane Reviews help people decide (Abstract) 2nd International Conference. Scientific Basis of Health Services & 5th Annual Cochrane Colloquium, October 1997.

(4) Battista RN, Hodge MJ. Setting priorities and selecting topics for clinical practice guidelines. Canadian Medical Association Journal 1995; 153:1233-7.

(5) Bradley R, Sankar C. Outcomes assessment: Electronic surveys versus paper-based surveys. Auburn University. 2003. Accessed at http://web6.duc.auburn.edu/research/litee/media/pdfs/eval_conf_papers/2003aseese_bradley.pdf on 30 January 2005.

(6) Brennan MRNPM. Survey-based experimental research via the Web: Some observations. Massey University, 83-92. 1999. Accessed at http://web6.duc.auburn.edu/research/litee/media/pdfs/eval_conf_papers/2003aseese_bradley.pdf on 30 January 2005.

(7) Canadian Medical Association. Implementing Clinical Practice Guidelines: A Handbook for Practitioners. 1997. Accessed at http://web6.duc.auburn.edu/research/litee/media/pdfs/eval_conf_papers/2003aseese_bradley.pdf on 30 January 2005.

(8) Field M, Lohr K (Eds). Clinical Practice Guidelines: Directions for a New Program. Washington, DC: National Academy Press, 1990.

(9) Gamis AS, Knapp JF, Glenski JA. Nitrous oxide analgesia in a pediatric emergency department. Annals of Emergency Medicine 1989; 18:177-81.

(10) Godambe SA, Elliot V, Matheny D, Pershad J. Comparison of propofol/fentanyl versus ketamine/midazolam for brief orthopedic procedural sedation in a pediatric emergency department. Pediatrics 2003; 112:116-23.

(11) Grounds RM, Lalor JM, Lumley J, Royston D, Morgan M. Propofol infusion for sedation in the intensive care unit: preliminary report. British Medical Journal Clinical Research Ed 1987; 294:397-400.

(12) Hoffman GM, Nowakowski R, Troshynski TJ, Berens RJ, Weisman SJ. Risk reduction in pediatric procedural sedation by application of an American Academy of Pediatrics/American Society of Anesthesiologists process model. Pediatrics 2002; 109:236-43.

(13) Kong KL, Willatts SM, Prys-Roberts C. Isoflurane compared with midazolam for sedation in the intensive care unit. British Medical Journal 1989; 298:1277-80.

(14) Lewis S. Paradox, process and perception: the role of organizations in clinical practice guidelines development. Canadian Medical Association Journal 1995; 153:1073-7.

(15) Margolis C, Cretin S (eds). Implementing Clinical Practice Guidelines. Chicago, Ill: AHA Press; 1999. 103.

(16) O'Sullivan GF, Park GR. The assessment of sedation in critically ill patients. Clinical Intensive Care 1990; 1:116-122.

(17) Ramsay MA, Savege TM, Simpson BR, Goodwin R. Controlled sedation with alphaxalone-alphadolone. British Medical Journal 1974; 2:656-9.

Appendices

Appendix 2.1: Search Strategy

For MEDLINE from 1966 to 2004, [1 procedural sedation.mp, 2 conscious sedation.mp, 3 conscious$.mp, 4 or/1-3, 5 exp emergency medicine/, 6 emergency medical services/, 7 emergency service, hospital/, 8 emergenc$.mp, 9 or/5-8, 10 exp hypnotics/ and sedatives/ 11 anesthetics/ 12 exp anesthetics, combined, 13 exp anesthetics, dissociative/, 14 exp anesthetics, general/, 15 exp anesthetics, inhalation/, 16 exp anesthetics, intravenous/, 17 exp narcotics/, 18 exp anti-anxiety agents/, 19 exp preanesthetic medication/, 21 or/10-20, 22 and/4,9,21] were used.

For EMBASE from 1988 to 2004, [1 exp anesthesiological techniques/, 2 conscious$.mp, 3 exp consciousness/, 4 or/1-3, 5 conscious sedation.mp, 6 procedural sedation.mp, 7 exp sedation/, 8 or/4-7, 9 exp premedication/, 10 exp emergency/, 11 exp emergency health service/, 12 exp emergency medicine/, 13 exp emergency surgery/, 14 exp emergency treatment/, 15 exp emergency ward/ 16 emergenc$.mp, 17 or/9-16, 18 exp hypnotic sedative agent/, 19 exp analgesic agent/, 20 exp anesthetic agent/, 21 exp tranquilizer/, 22 exp anesthesia/, 23 exp narcotic agent/, 24 or/18-23, 25 and/4,8,17,24, 26 (randome$ or placebo$ or met analy$ or metaanaly$).mp., 27 25 and 26, 28 (child$ or infan$ or newborn$ or youth$ or teen$ or adolescen$ or infan$.tw, 29 27 and 28] were used.

The 2004 2nd Quarter of CENTRAL/Cochrane Controlled Trials Register was searched, using the search terms: (((((PROCEDURAL and SEDATION) or (CONSCIOUS and SEDATION)) OR CONSCIOUSNESS) AND EMERGENC*) AND ((((((HYPNOTICS OR SEDATIVES) OR ANESTHETICS) OR NARCOTICS) OR (ANTI-ANXIETY AND AGENT)) OR (PREANESTHETIC AND MEDICATION)) OR (DENTAL AND ANESTHESIA))) [No restrictions]

For Dissertation Abstracts from 1861 – 2004, (KEY (anesthe?) OR KEY (sedat?) OR KEY(analges?) OR KEY(tranquilizer) OR KEY(narcotic) OR KEY(propofol) OR KEY (ketamine) OR KEY(fentanyl) OR KEY(etomidate) OR KEY (benzodiazepine?) OR KEY (morphine) OR KEY(nitrous oxide) OR KEY (chloral hydrate) OR KEY(Barbit?)) AND (KEY(Emergency) OR KEY(hospital) OR KEY(doctor) OR KEY(physician)) were used.

Appendix 2.2: Relevance form for inclusion (2 pages)

Reviewer: _______ Reference #: ______ Date:____-_____-____

Instructions: please complete the form on each study. If you reach a "no" response, exclude that study.

A. CRITERIA

	YES	**NO**	**Can't tell**
1. Study Design			
Were patients randomly assigned to receive treatment?	[ ]	[ ]	[ ]
2. Study Population			
Did the study include any paediatric patients (age < 18)?	[ ]	[ ]	[ ]
Were patients treated in a setting outside the OR?	[ ]	[ ]	[ ]
Did the study deal with procedures that are potentially painful or anxiety provoking?	[ ]	[ ]	[ ]
3. Study Intervention			
Did at least one patient group receive a sedative treatment during or immediately prior to the painful or anxiety provoking procedure?	[ ]	[ ]	[ ]
4. Outcome Measures			
Did the study consider one or more of the following outcomes?	[ ]	[ ]	[ ]

- Sedation score [ ]
- Pain Score or patient pain during the procedure [ ]
- Physiologic parameters (HR, BP, Sat, RR etc) [ ]
- Patient satisfaction [ ]
- Parent satisfaction [ ]
- Healthcare provider satisfaction [ ]
- Success of procedure [ ]
- Time needed to complete the procedure [ ]
- Ease of the procedure [ ]
- Occurrence of any adverse events [ ]
- Long-term outcomes [ ]

B. DECISION OF REVIEWER

Is this study potentially relevant for this review? [ ] [ ] [ ]

C. CONSENSUS OF ALL REVIEWERS

First independent review [ ]

Include [ ]

Exclude [ ]

Disagree

Re-review by two reviewers [ ]

Include [ ]

Exclude [ ]

Disagree

Final consensus by third party adjudication was to:

[ ] Include
[ ] Exclude

Appendix 2.3: Jadad Score, Allocation Concealment Score, and Quality of Concealment of Allocation (3 pages)

Quality Assessment of RCTs
Study # ______________ Initials of Assessor: ___

Part 1 Jadad Score(3)

Score

1. Was the study described as randomized (this includes the use of words such as randomly, random and randomization)?
   Yes = 1 No = 0 ______

2. Was the study described as double-blind?
   Yes = 1 No = 0 ______

3. Was there a description of withdrawals and drop-outs?
   Yes = 1 No = 0 ______

Additional points: Add 1 point if:

Method to generate the sequence of randomization was described and was appropriate (e.g. table of random numbers, computer generated, coin tossing, etc.) ______

Method of double-blinding described and appropriate (identical placebo, active placebo, dummy) ______

Point deduction: Subtract 1 point if:

Method of randomization described and it was inappropriate (allocated alternately, according to date of birth, hospital number, etc.) -______

Method of double-blinding described but it was inappropriate (comparison of tablet vs. injection with no double dummy) -______

OVERALL SCORE (Maximum 5) ______

Part 2: Allocation Concealment Score(9)

Concealment of treatment allocation:	☐ Adequate ☐ Inadequate ☐ Unclear

Adequate:	e.g. central randomization; numbered/coded containers; drugs prepared by pharmacy; serially numbered, opaque, sealed envelopes
Inadequate:	e.g. alternation, use of case record numbers, dates of birth or day of week; open lists
Unclear:	Allocation concealment approach not reported or fits neither above category

Part 3: Quality of Concealment of Allocation Score(1)

	POINTS
Allocation was not concealed (e.g. quasi-randomization)	0
Allocation concealment was not stated or was unclear	1
Disclosure of allocation was a possibility	2
Allocation was concealed (e.g. numbered, sealed opaque envelopes drawn NON consecutively)	3
Inclusion and exclusion criteria were not clearly defined in the text	0
Inclusion and exclusion criteria were clearly defined in the text	1
Outcomes of patients who withdrew or were excluded after allocation were NEITHER detailed separately NOR included in an intention to treat	0
Outcomes of patients who withdrew or were excluded after allocation were EITHER detailed separately OR included in an intention to treat analysis OR the text stated there were no withdrawals	1
Treatment and control groups were NOT adequately described at entry	0
Treatment and control groups were adequately described at entry: A minimum of 4 admission details were described (e.g. age, sex, mobility, type of surgery, ASA grade, function score, mental test score)	1
The text stated that the care programmes other than trial options were NOT identical	0
The text stated that the care programmes other than trial options were identical	1
Outcome measures were NOT clearly defined in the text	0
Outcome measures were clearly defined in the text	1
Outcome assessors were NOT blind to the allocation of patients	0
Outcome assessors were blind to the allocation of patients	1
The timing of the measurement of the outcomes was NOT appropriate	0
The timing of the measurement of the outcomes was appropriate	1
TOTAL NUMBER OF POINTS:	**/ 10**

Appendix 2.4: Data Extraction form (9 pages)

Initials of Assessor: _________ Date: _______________
Initials of 2nd Assessor: _________ Date: _______________

Study ID:
Authors:
Medline Journal ID:
Year of Publication:
Language/Country:
Sponsorship: Pharmaceutical __ Government __ Private __ Other ___________
Study Design: Parallel __ Crossover __ Cluster __ Other ________________________
Comments:

METHODS:

Randomization Method: Page/para: _______

Subject -Blinded Yes_____ No_____ Unclear_____

Physician - Blinded Yes_____ No_____ Unclear_____

Outcome Assessor –Blinded Yes_____ No_____ Unclear_____

PARTICIPANTS: Page/para: ______

Number of eligible participants: Number enrolled in study:

Number of pediatric patients (<17): Age Range of Patients:

SETTING: Page/para: _______

Emergency Department: _____	Clinic: _____	Dental surgery: _____
Ward: _____	Intensive Care Unit: _____	Other (specify): ______

TYPES OF PROCEDURES (Tick all that apply): Page/para: _______

Orthopedic _____	Lacerations _____	Dental _____
Imaging _____	LP/BMA _____	Other (specify) _______

INTERVENTION: Page/para: _______

	Drug	Dose	Route	Duration	Co-intervention(s)
Treatment Group 1					
Treatment Group 2					
Treatment Group 3					

COMMENT ON TREATMENT:

WITHDRAWALS: Page/para: _______

Withdrawals described? Yes_____ No_____ Unclear_____

Treatment group	# Withdrawn	Reason
1		
2		
3		

Was an Intention-to-treat protocol followed? Yes ___ No ___ Unclear ___ Page/para: _____			

OUTCOMES:

Treatment Group 1:
Treatment:____
Number of patients (n) = _____

	Mean:	SD/SE (specify):	95% Conf. Int.	p value	Other (specify)	Page/ para
Sedation score: Specify/define:______ Validated? Yes __ No __ Unclear __						
Pain score: Specify/define:_______ Validated? Yes __ No __ Unclear __						
Distress score: Specify/define:______ Validated? Yes __ No __ Unclear __						
Heart rate:						
Blood pressure:						
Respiratory rate:						
Oxygen saturation:						
Glasgow Coma Score:						
Other physiologic parameter(s) (specify ____________________)						
Patient satisfaction: Specify/define:______ Validated? Yes __ No __ Unclear __						
Parent satisfaction: Specify/define:____ Validated? Yes __ No __ Unclear __						
Healthcare worker satisfaction: Specify/define:_____ Validated? Yes __ No __ Unclear __						

Success/ease of procedure: Specify/define:___ Validated? Yes __ No __ Unclear __						
Time to discharge:						
Time needed to complete the procedure:						
Overall adverse events:						
Respiratory adverse events: Specify ______						
Cardiovascular adverse events: Specify _____						
Vomiting:						
Psychological adverse events: Specify _____						
Other adverse events: Specify ___						

OUTCOMES:

Treatment Group 2:
Treatment:____
Number of patients (n) = _____

	Mean:	SD/SE (specify):	95% Conf. Int.	p value	Other (specify)	Page/ para
Sedation score: Specify/define:______ Validated? Yes __ No __ Unclear __						
Pain score: Specify/define:_______ Validated? Yes __ No __ Unclear __						
Distress score: Specify/define:______ Validated? Yes __ No __ Unclear __						
Heart rate:						
Blood pressure:						
Respiratory rate:						
Oxygen saturation:						
Glasgow Coma Score:						
Other physiologic parameter(s) (specify ___________________)						
Patient satisfaction: Specify/define:______ Validated? Yes __ No __ Unclear __						
Parent satisfaction: Specify/define:____ Validated? Yes __ No __ Unclear __						
Healthcare worker satisfaction: Specify/define:_____ Validated? Yes __ No __ Unclear __						
Success/ease of procedure:						

Specify/define:___ Validated? Yes __ No __ Unclear __						
Time to discharge:						
Time needed to complete the procedure:						
Overall adverse events:						
Respiratory adverse events: Specify ______						
Cardiovascular adverse events: Specify _____						
Vomiting:						
Psychological adverse events: Specify _____						
Other adverse events: Specify ___						

OUTCOMES:

Treatment Group 3:
Treatment:____
Number of patients (n) = _____

	Mean:	SD/SE (specify):	95% Conf. Int.	p value	Other (specify)	Page/ para
Sedation score: Specify/define:______ Validated? Yes __ No __ Unclear __						
Pain score: Specify/define:_______ Validated? Yes __ No __ Unclear __						
Distress score: Specify/define:______ Validated? Yes __ No __ Unclear __						
Heart rate:						
Blood pressure:						
Respiratory rate:						
Oxygen saturation:						
Glasgow Coma Score:						
Other physiologic parameter(s) (specify ___________________)						
Patient satisfaction: Specify/define:______ Validated? Yes __ No __ Unclear __						
Parent satisfaction: Specify/define:____ Validated? Yes __ No __ Unclear __						
Healthcare worker satisfaction: Specify/define:_____ Validated? Yes __ No __ Unclear __						
Success/ease of procedure: Specify/define:___						

Validated? Yes __ No __ Unclear __						
Time to discharge:						
Time needed to complete the procedure:						
Overall adverse events:						
Respiratory adverse events: Specify ______						
Cardiovascular adverse events: Specify _____						
Vomiting:						
Psychological adverse events: Specify _____						
Other adverse events: Specify ___						

SUBGROUP ANALYSES & RESULTS:

CHANGES IN PROTOCOL:

CONTACT WITH AUTHOR:

OTHER COMMENTS ON THIS STUDY:

Appendix 3.1: Children's Hospital of Eastern Ontario Pain Score (CHEOPS) (7)

Cry (1-3)
Facial expression (0-2)
Verbal remarks (0-2)
Torso movement (1-2)
Leg movement (1-2)
Reaching (1-2)

Range of possible scores: 4-13

Appendix 3.2: Observational Score of Behavioral Distress Revised (OSBDR) (2;4-6)

A revised version of the Procedural Behavior Rating Scale(45), designed for use with BMAs.

11 behaviours indicative of anxiety and/or pain in children (respective intensity weights):

Cry (1.5)
Scream (4.0)
Physical restraint (4.0)
Verbal Resistance (2.5)
Requests emotional support (2.0)
Muscular rigidity (2.5)
Verbal Fear (2.5)
Verbal Pain (2.5)
Flail (4.0)
Nervous behaviour (1.0)
Information seeking (1.5)

Appendix 3.3: Ramsay Sedation Score (8)

Awake
1 = anxious and agitated or restless
2 = cooperative, oriented, and tranquil
3 = responds to commands only

Asleep
4 = brisk response to light glabellar tap or loud auditory stimulus
5 = sluggish response to light glabellar tap or loud auditory stimulus
6 = no response to light glabellar tap or loud auditory stimulus

Score	**Interpretation**
1	Inadequate sedation
2, 3 or 4	Acceptable sedation
5 or 6	Excessive sedation

Reference List for Appendices

(1) Cracknell J, Bismuth LMAM, Pedersen T, Pace N, Heick S. Tips for reviewers. The Cochrane Anaesthesia Review Group, 2003.

(2) Elliott CH, Jay SM WP. An observational scale for measuring children's distress during medical procedures. J Pediatr Psychol 1987; 12, 543-551.

(3) Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Controlled Clinical Trials 1996; 17:1-12.

(4) Jay S, Elliot C. Behavioral observation scales for measuring children's distress: the effects of increased methodological rigor. J Consult Clin Psychol 1984; 52, 1106-1107.

(5) Jay SM, Ozolins M ECCS. Assessment of children's distress during painful medical procedures. Health Psychol. 1983; 2:133-147.

(6) Katz E, Kellerman J, Siegel S. Behavioral distress in children undergoing medical procedures: developmental considerations. J Consulting and Clinical Psychology 1980; 48, 356-365.

(7) McGrath PJ, Johnson G, Goodman JT, et al. CHEOPS: a behavior scale for rating postoperative pain in children. In: Fields HL, Dubner R, Carvero Feal, editors. Advances in Pain Research and Therapy. New York, NY: Raven Press, 1985: 395-402.

(8) Ramsay MA, Savege TM, Simpson BR, Goodwin R. Controlled sedation with alphaxalone-alphadolone. British Medical Journal 1974; 2:656-9.

(9) Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. JAMA 1995; 273:408-12.